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LOCAL CANCER CHEMOTHERAPY

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LOCAL CANCER CHEMOTHERAPY may be defined as the regional placement of chemotherapeutic agents by physical means. Its purpose is to minimize the effects on organs outside of the tumor zone and to permit the delivery of a higher dose to the tumor cells. The experience with radiation therapy has shown that by proper localization doses 50 to 100 times higher than those safely given by total body radiation can be delivered. If the same accuracy in localization and dosimetry could be achieved with chemotherapy as with radiation therapy, the scope of cancer chemotherapy would be greatly extended.

Local chemotherapy in the form of surface applications of caustic agents was the first effective method for treating cancer. Haagensen (62) states that Hippocrates reported results which would be termed "encouraging" according to today's cancer reports. Other types of local chemotherapy, such as interstitial, intravascular, and intracavitary injections, have also been tried for a long time. Fascinating reports on the local use of chemical agents can be found in the medical literature of the nineteenth and early twentieth centuries, e.g., Moore (91), 1866; Broadbent and Randall (24), 1866; Biggs (17), 1880; Carpenter (28), 1880; Bulkley (27), 1894; Allen (4), 1903; and Stone (125), 1916. It is also interesting to note that mustard gas in solution was used by Adair and Bagg (2) for surface and interstitial tumor applications at the Memorial Hospital in 1931, which was more than 10 years before the nitrogen mustards were first employed for systemic cancer chemotherapy.

Many reports on local applications of modern chemotherapeutic agents have been published since 1950. Although initial tumor regression has usually been observed, the results in general have been unpredictable and recurrences have been frequent. The present situation appears to us to be similar to that of cancer therapy with roentgen rays and radium in its first decade. Good results then were rare and side reactions frequent, as they are today with local chemotherapy. Only after the distribution and dose had been accurately controlled did radiation therapy give consistently worthwhile results. We therefore anticipate that local chemotherapy will also become a valuable tool in cancer management after techniques for better distribution and dose control are perfected. This article is written in the hope of stimulating interest in local chemotherapy by reviewing the published reports and by pointing out possibilities for improving local chemotherapy applications.

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The different possibilities for local cancer chemotherapy are classified for this discussion into: (1) surface applications, (2) intravascular applications, (3) interstitial applications, and (4) agents for local chemotherapy. Abbreviations, which are defined in Table I, are used for the most widely employed chemotherapeutic agents.

SURFACE APPLICATIONS

Chemotherapeutic agents may be applied to skin, to mucosal surfaces, and to surfaces of natural cavities, such as the pleura and the peritoneum, or to surfaces of artificially created spaces, such as wounds. The purpose may be to cure, to provide palliation, or to prevent local recurrences if all gross cancer is surgically removed. For this review, the surface applications will be discussed under the following three headings: (a) treatment of superficial tumors, (b) treatment of malignant effusions, and (c) prevention of local recurrences.

Treatment of superficial tumors. The use of chemical agents for the treatment of superficial tumors has been recorded as early as the Fifth Century B.C. by Hippocrates. A critical survey of this form of cancer therapy can be found in Stone's 1916 article entitled "A Review of the History of Chemical Therapy in Cancer," in which he concluded that the evidence of the value of chemical caustics was sufficiently strong to justify a new study and that the caustic agents might afford a valuable adjuvant to the use of the knife.

Today caustic agents are still widely used. For instance, Hoxsey (68) claims in his book, *You Don't Have to Die*, that prominent medical witnesses in recent court proceedings had to concede that he had accomplished cures with his pastes in histologically proved cancer.

The technique of surface applications of chemical agents has been developed to a high degree of perfection by Frederic E. Mohs at the University of Wisconsin. In 1956 he published a 292 page book with details of his technique and results based on more than 20 years' experience (90). Mohs fixes a tissue layer of about 2 millimeters depth with a 45 per cent zinc chloride paste. He then excises the fixed tissue and examines it microscopically. Whenever cancer is found, the application of the zinc chloride paste is repeated until a depth is reached at which there is no microscopic evidence of cancer. In this way, a minimum amount of normal tissue is sacrificed.

The initiative for the first trial of modern chemotherapeutic agents for surface applications in cancer must be credited to James Ewing. While at the Army Institute of Pathology during the First World War, Ewing was impressed by the peculiar histologic reactions to mustard gas. In 1927, as director of the Memorial Hospital in New York, he interested Halsey J. Bagg in animal experiments with mustard gas. These experiments, together with clinical observations in 13 patients, were reported in 1931 by Adair and Bagg (2). Twelve of the patients were treated by superficial applications of mustard gas dissolved in water. One patient was treated by interstitial injection of this solution; this case will be discussed later. The 12 patients included 4 patients with carcinoma of the penis, 3 with epitheliomas of the skin, 2 with melanomas, 1 with a neurofibroma, 1 with a wart, and 1 with a pigmented nevus. Adair and Bagg stated that they saw no recurrence several months after the application of the mustard gas solution, and that the scars were pliable, well healed, and painless. This study was discontinued after Bagg contracted pneumonia from inhalation of the mustard gas.

Surprisingly, we have not been able to find another report on the local treatment of skin tumors with modern chemotherapeutic agents since the study of Adair and Bagg was published in 1931. The lack of work in this field is regrettable for two reasons: (1) Superficial tumors would provide an excellent opportunity to study the response of human neoplasms as well as normal tissues to the modern chemotherapeutic agents, and (2) surface application of suitable chemotherapeutic agents might prove to be a worthwhile addition to our arsenal for the treatment and prevention of skin cancer. In most instances of skin cancer, surgical excision or local roentgenotherapy will, of course, remain the treatment of choice. However, for multiple precancerous skin changes and for multiple superficial skin cancers, such as are frequently seen in "sailor's skin" after prolonged exposure to the short-wave ultraviolet rays of the sun, local surface applications of modern chemotherapeutic agents might prove satisfactory. Their use would provide a most economical treatment. It could be of special value in tropical and subtropical parts of the world where a light-skinned popu-

TABLE I.—NOMENCLATURE OF CHEMOTHERAPEUTIC AGENTS

Group names	*Abbreviations*	*Year placed in clinical trial*	*Chemical name*	*Synonyms*
	HN_2	1946	Methyl bis-(beta-chloroethyl) amine hydrochloride	Mechlorethamine hydrochloride; mustargen; embichin
	TEM	1950	2, 4, 6-Tris(ethylenimino)-s-triazine	Triethylene melamine
	Myleran	1951	1, 4-Dimethanesulfonoxybutane	Busulfan; G.T. 41
Alkylating agents*.....	HN_2O	1952	Methyl-bis-(beta-chloroethyl) amine N-oxide hydrochloride	Nitromin; mitomen; MBAO; N-oxide mustard
	TEPA	1953	Triethylene phosphoramide	
	TSPA	1953	Triethylene thiophosphoramide	THIOTEPA
	PAM	1953	p-Di-(2-chloroethyl) aminophenylalanine	Phenylalanine nitrogen mustard; racemic form-sarcolysin L-isomer; CB-3025; melphalan
	Cytoxan	1958	2H-1,3,2-Oxazaphosphorine, 2-(bis[2-chloroethyl]amino) tetra-hydro-, 2-oxide	Endoxan
Antimetabolites				
Folic acid antagonists.....	Aminopterin	1948	4-Amino-pteroylglutamic acid	
	Amethopterin	1949	4-Amino-N 10-methylpteroylglutamic acid	Methotrexate
Nucleic acid antagonists.....	6-MP	1953	6-Mercaptopurine	Mercaptopurine; purinethol
	5-FU	1958	5-Fluorouracil	Ro 2-9757
	5-FUR	1959	5-Fluorouridine	
	5-FUDR	1959	5-Fluoro-2′-deoxyuridine	
Antibiotics.....	Act.-D	1957		Actinomycin D
Chemical warfare agents.....	Mustard gas	1931	Dichlorodiethyl sulfide	
	Lewisite I		Chlorovinyldichloroarsine	
	Lewisite II		Dichlorodivinylchloroarsine	

*Synonyms: Azotoyperites, NM, Stickstofflosts, N Losts. These terms are also often used for HN_3.

lation is exposed to intensive sun, as for instance in Australia. Surface applications may also be worth a trial in very superficial intraoral lesions.

In our review of the literature, 5 reports were encountered which describe the use of surface applications for cancers in other locations than the skin. Bateman (11) in 1955 mentioned 1 patient with bladder carcinoma who was treated by intravesical instillation of TSPA. Subsequently, cancer cells disappeared from the urine. This type of local chemotherapy appears worthy of consideration in very superficial bladder carcinomas which involve all or most of the bladder mucosa and which are not suitable for total cystectomy. In early cases, it might accomplish as much as the direct instillation of a radioactive solution, such as colloidal radioactive gold, Au^{198}, into the bladder. In later stages, radioactive solutions would probably be preferable because they have a better depth effect.

The second report is that of Schulze (111) in 1957 on the treatment of 2 patients with rectal carcinoma who were not suitable for operation. Daily enemas of tetramin were given in addition to oral tetramin therapy. Schulze reported "apparent cure" in 1 patient and good regression in the other. There will be few such cases available in view of the present status of anesthesia, surgery, and radiation therapy. However, Schulze's report indicates that the intraintestinal use of chemotherapeutic agents should be explored.

The third and fourth reports are those of Whiteside, Philips, Dargeon, and Burchenal (138) in 1958 and Murphy (99) in 1959 on the intrathecal use of methotrexate at the Memorial Center in New York City. Much higher doses could be administered in this way than with systemic application and better results were achieved in cases of involvement of the central nervous system by leukemia and lymphoma than with intravenous injections.

The fifth report is that of Rousselot and Cole (105) in which they discuss the results in a series of patients treated at the St. Vincent's Hospital in New York City in 1960 and 1961. They have developed a new technique to permit a more direct action on the tumor cells and

the metastases; namely, the intraluminal or topical use of chemotherapeutic agents as an adjunct to operation. The tumor bearing area of the gastrointestinal tract is immediately isolated at the beginning of the surgical procedure. The drug is introduced into the lumen of the isolated segment. Aliquots taken from the specimen and the veins draining the area indicate good adsorption and absorption during the operation. To date this procedure has been performed on 10 patients without demonstrable adverse effects locally or systemically. It appears as a worthwhile attempt to prevent local recurrences and metastases from surgical manipulation. This technique offers unique possibilities for precise dosimetry and localization to the tumor area.

Treatment of malignant effusions. The first report on the intracavitary use of a modern chemotherapeutic agent for the suppression of malignant effusions is contained in an article by Karnofsky, Abelmann, Craver, and Burchenal (72) in 1948. The authors state in their summary: "Our brief experience with the intrapleural injection of HN_2 in patients with metastases to the pleura and recurrent pleural effusions has demonstrated that the technique is simple, and the reactions at the site of injection are not necessarily severe. Under the proper conditions, presumably when the absorption of HN_2 from the pleural space is retarded, a decrease in pleural effusion may occur (case 30); if absorption is rapid, the agent appears to be without local effect (case 14)."

Unfortunately, this observation, presented as part of a general review entitled "The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma," did not stimulate further work in this field. Only after the use of radioactive colloids for the suppression of fluid formation had become popular was intracavitary injection of chemotherapeutic agents taken up again.

Since the use of radioactive colloids has overshadowed the intracavitary application of chemotherapeutic agents, we shall briefly review the experience with radioactive colloids. This provides a yardstick to judge the value of intracavitary injection of chemotherapeutic agents for the same purpose. A detailed review of the intracavitary use of radioactive colloids with bibliography up to September 1958 has been presented by Henschke, Card, Cole, and Placek (64).

The originator of this technique is J. H. Müller of Switzerland. He first used cyclotron-produced radioactive zinc in colloidal suspension, Zn^{63}, in 1945 (96). In 1950, Müller (97) turned to pile-produced colloidal radioactive gold, Au^{198}, which had been developed by Sheppard, Goodell, and Hahn (115) in 1947. As a result of the research program of the Atomic Energy Commission, many studies were soon carried out on this promising application. Other isotopes were also studied. The use of chromic radioactive phosphorus, P^{32}, was reported in 1950 by Jaffe (70) and the use of radioactive yttrium, Y^{90}, was described by Siegel and his colleagues (118) in 1956.

A survey of the results of treatment with radioactive colloids, of a total of 1,779 patients reported in the world literature up to September 1958 showed suppression of fluid formation in 488 or 54 per cent of 895 intrapleural applications, in 378 or 50 per cent of 760 intraperitoneal applications, and in 6 or 86 per cent of 7 intrapericardial injections (63).

Chemotherapeutic agents are desirable for the treatment of malignant effusions because of their low price and the absence of storage, supply, licensing, and radiation safety problems, which plague the use of radioisotopes. These practical aspects have promoted the premature use of chemotherapeutic agents. In contrast to the well-documented results of treatment of a large number of patients with radioactive colloids, the reports on the intracavitary use of chemotherapeutic agents leave much to be desired. Those reviewed by us are compiled in Table II. Many investigators do not report the number of patients benefited by the procedure or even the total number of patients treated. Omitting these, a total of 372 cases are recorded, in 234 or 63 per cent of which the patients are said to have received some benefit from the procedure. The figures for the percentage of benefited patients out of total number of patients are 152 of 237 or 64 per cent for pleural effusions, 48 of 83 or 58 per cent for peritoneal effusions, and 10 of 10 or 100 per cent for pericardial effusions.

Although the percentage figures compare favorably with those for the radioactive colloids, the use of chemotherapeutic agents for the treatment of malignant effusions cannot yet be considered well founded. It is uncertain how much of the agent reacts in the cavity and how much

TABLE II.—INTRACAVITARY INJECTION

Author	Year	Agent	Dosage, mgm.	Improved/total patients: Pleura	Peritoneum	Pericard.	Cer. sp. fluid	Bladder	Rectum	Total
Karnofsky *et al.* (72)	1948	HN_2		1/2						1/2
Albertelli *et al.* (3)	1953	HN_2								
Bateman (11)	1955	TSPA mainly	10–30 1–14×	12/16	5/8	1/1		1/1		19/26*
Weisberger *et al.* (135)	1955	HN_2	10–20 single dose	18/30	8/11	2/2				28/43
Bonte *et al.* (20)	1956	HN_2 Au^{198}	0.2 =0.4	4/4	3/7	1/1				8/12
		HN_2	per kgm.	18/30	7/10					25/40
Sattler (109)	1957	E 39	5	?/118						?/118
Schulze (111)	1957	Tetramin	250 daily						1/?	1/?
Ultmann *et al.* (131)	1957	TSPA	20–50 single dose	?/3	?/1	?/1				?/5
Wright (141)	1957	TSPA	10–40 1–5×	?/2	?/4					?/6
Bateman (12)	1958	TSPA	10–60	33/42	2/4	2/2				37/48
		ODEPA	15–80							
Franco *et al.* (53)	1958	Prednisone		9/17	7/11					16/28
Fullerton and Reed (54)	1958	HN_2	10							4/8
Leone *et al.* (83)	1958	TSPA	1.5–2.5/kgm., 1–2 wks.	5/8	0/2	1/1				6/11
Schell and Hall (110)	1958	TSPA	20–40							
		TEM	5–10							
Weisberger (132)	1958	HN_2	10–20 single dose	37/55	16/30	3/3				56/88
Whiteside *et al.* (138)	1958	Methotrexate	0.1–0.5/kgm.				5/5			5/5
Dale (42)	1959	TSPA	30–80	14/28†						14/28
		HN_2	30–40	15/33						15/33
Mrazek *et al.* (95)	1959	TSPA	95 av.t.d.							
		Nitromin	200–800 total ds.	2/?						2/?
Total:				152/237	48/83	10/10	5/5	1/1		234/372
Per cent				64	58	100	100	100		63

*Two patients received injections by more than one route.
†Includes both pleural and peritoneal injections.

escapes into the circulation. Leone, Hansbarger, Nolley, and Mellette (83) reported in 1958 that with thioTEPA a blood response was observed as frequently in intracavitary administration as in intravenous treatment. Graef, Karnofsky, Jager, Krichesky, and Smith (59) in 1948 found that the median lethal dose of HN_2 by intraperitoneal injection is only slightly higher than by intravenous injection—2.3 mgm./kgm. versus 2.0 mgm./kgm. The general impression is that HN_2 is for the most part retained in the cavity whereas other agents, such as TSPA, reach the circulation in large amounts. However, this is not documented by experimental or clinical observations. It is also not clear whether rapid-acting agents, such as HN_2, produce marked adhesions with the customary doses. In mice high doses of HN_2, e.g., 0.08 milligrams in 20 gram mice, administered intraperitoneally produce severe peritoneal reactions with loops of the intestines becoming matted into inseparable masses, as we found in experiments conducted with Ruben Oropeza. Chambers (29) intentionally obliterated the pleural space by causing adhesions with talcum powder. Although adhesions in the pleural cavity may be useful in certain situations, in the peritoneal cavity they appear undesirable and dangerous.

Clinical observations also indicate the need for further studies before the use of chemotherapeutic agents can be generally recommended. Weisberger, Levine, and Storaasli (135) noted that pain occurs after the intracavitary use of HN_2. Although pain was rarely associated with intrapleural injections, it was a common occurrence with the intra-abdominal administration. Nausea, vomiting, sleepiness, dryness of the mouth, and leukopenia are other side effects which have been observed after intracavitary injections of HN_2. These reactions indicate a definite systemic effect. A further reason for caution in the use of chemotherapeutic agents is the fatal reactions which have occurred after the intracavitary use of HN_2. On the Radiation Therapy Service of the Memorial Center, 3 patients died suddenly within 8 to 96 hours after intrapleural injection of 22.4 to 24.4 milligrams of nitrogen mustard. Unfortunately, in no case was permission for autopsy granted so that other causes of death, especially traumatic tension pneumothorax, could not be ruled out. However, no such early deaths have occurred with

the intracavitary use of radioisotopes although more patients have been treated with radiocolloids than with chemotherapeutic agents.

Prevention of local recurrences. Local recurrences are the cause of failure in many cancer operations. Their development from implanted cancer cells was recognized by many medical pioneers. Moore (92) in 1867 commented specifically on the danger of "seeding." For the prevention of local recurrence, Lack (82) in 1896 recommended carbolic acid spray, and Babler (7) in 1909 was using alcohol and other chemicals in operative wounds. Mayo (87) in 1913 suggested the local use of phenol or cautery if complete extirpation was not possible. Ewing (49) in 1933 recommended that a biopsy wound for mammary cancer be closed over a sponge soaked in 10 per cent formalin to prevent spillage of viable tumor cells during subsequent dissection.

It has now been demonstrated conclusively that cells of a malignant neoplasm are constantly being cast off into the body cavity. Reports have been made by Smith and Hilberg (119); Dahle (41); Spjut, Hendrix, Ramirez, and Roper (120); Quan (102), and Moore and his colleagues (93). Of a total of 342 patients obtained by combining the first 4 reports, malignant cells were found in the wound or the abdominal cavity during cancer operations in 23 per cent. Cells which were suggestive of malignancy but could not be classified definitely as malignant were found in an additional 11 per cent.

The percentage of positive washes for malignant cells in the cavity depends on the stage of the tumor, as shown by the study of Moore and his associates (93) in 1959. Of 251 patients with abdominal cancer, positive washings were observed in noncurable cancer in 66 per cent (stomach), 58 per cent (colon), and 43 per cent (rectum); whereas in curable cancer, positive washings were found in 33 per cent (stomach), 32 per cent (colon), and 16 per cent (rectum).

Many investigators, including Saphir (108), McGrew, Laws, and Cole (88), Ackerman and Wheat (1), Smith and Hilberg (119), and Knox (77), have demonstrated that the shedding of cells is accentuated by manipulation.

Radioactive colloids were used for the prevention of local recurrences, as for the treatment of malignant effusions, before chemotherapeutic agents were tried. A brief discussion of the work with radioactive colloids therefore appears valuable as a basis for evaluating chemotherapeutic agents in the prevention of local recurrences. A detailed review of this work has been presented elsewhere (64).

A number of studies have shown that radioisotopes in colloidal form injected into the cavity destroy malignant cells. Goldie and Hahn (56) in 1950 observed the disappearance of sarcoma 37 cells in the peritoneal fluid of mice 48 to 72 hours after the injection of colloidal Au^{198}. In clinical studies, Stembridge, Kniseley, and Andrews (124) and Wheeler, Jaques, and Botsford (136) reported a decrease in the number of tumor cells as seen in cell blocks after administration of colloidal Au^{198}.

The only figures on end results with the prophylactic use of radioisotopes were published in 1959 by Müller (98), who originated the method in 1945. He has used radioactive gold, Au^{198}, postoperatively in cancer of the ovary since 1950. Fifty-one of his cases are available for a 5 year analysis. In 10 of these, all gross tumor was removed and all of these patients are alive and well at 5 years—an unusual result for ovarian carcinoma.

Our own clinical experience with the prophylactic use of radiocolloids through the end of 1958 included 151 patients. Colloidal radioactive phosphorus, P^{32}, was used in most of these cases because it has a number of practical advantages over Au^{198}. Fifty of our patients had carcinoma of the ovary, 38 had cancer of the lung, 22 cancer of the cervix, 11 cancer of the colon, 6 cancer of the stomach, and 6 cancer of the uterus. The remaining 18 patients are classified as having miscellaneous neoplasms. In 139 patients, gross tumor was left behind at the time of operation. These patients, therefore, cannot be used to evaluate the method, since recurrence might be on the basis of residual tumor. In only 12 patients no gross tumor was left behind, and no recurrence has been demonstrated thus far. They have been followed up and are alive and well at 13, 14, 18, 18, 20, 22, 27, 27, 28, 31, 34 (radioactive gold used in this patient), and 36 months. This group includes 7 patients with ovarian carcinoma, who are alive and well 13 to 36 months after treatment. In 3 of these cases of ovarian tumor, rupture and spillage occurred at operation.

The use of chemotherapeutic agents in place of radiocolloids for the prevention of local recurrences appears attractive because it is more

economical and poses no problems of radiation safety, supply, and licensing. Ship, Eck, and Smith (116) in 1958 demonstrated the possible effectiveness of a 0.05 per cent formaldehyde solution. This material applied at times varying from 5 minutes before to 24 hours after tumor inoculation prevented growth of tumor in 80 to 85 per cent of the mice. Of the untreated controls, tumor growth occurred in 100 per cent. Treated mice in which tumor developed demonstrated a significant delay in time of appearance of tumor. The same concentration of formaldehyde placed in the wound 1 to 24 hours prior to tumor inoculation resulted in enhanced growth of tumor.

Seal (112) in 1958 at the Memorial Center compared chemotherapeutic agents with radiocolloids in transplantable ascites rat tumor. These agents were introduced into the peritoneal cavity at the same time as the tumor cells. In all animals in which only the ascites tumor was injected cancer developed and death occurred. When HN_2 was injected at the same time as the implant, 80 per cent of the animals survived; when radioactive colloidal gold was used, 92 per cent survived; and when radioactive colloidal phosphorus was used, 96 per cent survived.

Kramer, Eck, and Smith (79) studied the prevention of S-91 melanoma and sarcoma 37 in mice by the use of TSPA. When TSPA was given in the tumor inoculation site at or shortly after the time of inoculation, the tumors were smaller than those in the control group. This effect was greater when tumor and TSPA were given intraperitoneally than when they were given intramuscularly. Krementz, Kerlin, and Leonard (80) also investigated the effectiveness of TSPA in preventing tumor growth. They instilled Brown-Pearce tumor cells in the subcutaneous abdominal incisions of 94 rabbits. Of the control group 79 per cent of the animals had growth in the wound. Of the group treated with TSPA intraperitoneally, 81 per cent had tumor growth. The group in which the wound was irrigated with saline showed tumor growth in 74 per cent. Of the group treated with TSPA instilled locally in the wound, only 40 per cent showed tumor growth. Cohn and Atik (32), conducted experimental studies in rabbits and have suggested the value of considering chemotherapeutic agents injected directly into the lumen of the bowel to limit the spread of tumor cells during operation.

Whitehead, Lanier, and Thompson (137) experimented with HN_2 combined with radiogold to inhibit the growth of Ehrlich ascitic carcinoma in mice. The inoculations were given intraperitoneally and treatment was begun on the following day. The effectiveness was judged by the number of cells in the ascitic fluid. The authors were of the opinion that the HN_2-radiogold combination caused more tumor inhibition than would be anticipated if the effect of the two agents was merely an additive one.

On the basis of their own animal experiments, Cole and his co-workers (94) at the University of Illinois Medical Center started a program of prophylactic and adjuvant injection of nitrogen mustard immediately after curative resection of carcinoma in the hope of reducing the rate of local recurrences and distant metastases. This was expanded under the auspices of the Cooperative Clinical Research Program of the Cancer Chemotherapy National Service Center into a large co-operative study. Int his program 25 per cent of the full dose of HN_2 or TSPA was placed in the pleural or peritoneal cavity during operation, the other 75 per cent intravenously. In that part of the study conducted at Veterans Administration hospitals, the 30 day mortality was significantly higher in the treated group than in the control group—22 per cent versus 7 per cent for lung cancer, 23 per cent versus 10 per cent for gastric cancer, and 12 per cent versus 2 per cent for colorectal cancer (36). Since most of the agent was given intravenously, the effects of the intracavitary applications cannot be evaluated from this study. We hope that the value of intracavitary use of radiocolloids and chemotherapeutic agents without additional systemic chemotherapy will be tested soon in a controlled clinical study.

INTRAVASCULAR APPLICATIONS

For this review the intravascular applications will be discussed under the following three headings: (a) intravenous injections with localized effects, (b) intra-arterial injections, and (c) perfusion.

Intravenous injections with localized effects. Intravenous injection will produce a localized effect if the injected drug loses its toxicity rapidly and/or becomes fixed in the tissue supplied by the first capillary system. In this way a localization effect is probably produced in the lungs. Boyland, Clegg, Koller, Rhoden, and Warwick

(22) observed in 1948 that cancer of the lung showed greater response to the intravenous administration of HN_2 than did cancers in other parts of the body. Klopp, Alford, Bateman, Berry, and Winship (76) pointed out that this may be explained by the rapid detoxification of HN_2. Distribution studies in mice by Seligman, Friedman, and Rutenburg (113) in 1950 with HN_2-labeled radioactive iodine also showed that HN_2 reacts very rapidly and that uncyclicized HN_2 reaches only the lung tissues intact.

Injection of a tributary of the portal vein may be expected to produce a similar effect on cancer in the liver and was first described by Mrazek and his associates (94) in 1959.

Another possibility to produce a localized effect with intravenous injection is to exclude parts of the body from the general circulation. Placing tourniquets around all extremities for this purpose was, to our knowledge, first suggested by Klopp and his co-workers in 1950 (76). This method is frequently used at our hospital for intravenous nitrogen mustard therapy. We do not know of any studies on the actual value of this procedure. It may be worthless, since the usual tourniquets decrease the blood flow to the distal parts of the extremities where little if any active bone marrow is located in the adult. The principle, however, is sound and should be explored further. Temporary occlusion of the abdominal aorta by outside clamps, such as those used in obstetrics, or by balloons introduced from the femoral artery into the aorta is a readily available means of restricting an agent to one-half of the body. Miller (89) at the Memorial Center has recently shown that with a balloon inserted into the aorta and kept inflated for 10 minutes, much higher doses of HN_2 can be administered.

Intra-arterial injections. In 1950, Klopp, Alford, Bateman, Berry, and Winship (76) published a noteworthy article on the intra-arterial use of chemotherapeutic agents. They clearly outlined a number of principles for the further development of intra-arterial injection, namely, (1) repeated intra-arterial injections of small doses to increase the selectivity of the effect, (2) intravenous injection of a nontoxic antagonist at the time of intra-arterial injection of the chemotherapeutic agent to reduce systemic toxicity, and (3) use of a heart-lung mechanical pump to maintain the circulation of an isolated tumor-bearing area, a technique now usually termed perfusion, in contrast to intra-arterial injection, which is now referred to as infusion.

Table III gives a brief review of the literature on intra-arterial injections with chemotherapeutic agents. Most patients treated by this method had advanced cancer in various areas of the body. Some reports do not give complete results. Omitting these, some improvement is claimed in 136 patients, or 63 per cent, of a total of 215 patients. The most frequent beneficial effect was relief of pain in pelvic tumors. Only a few long term improvements are reported. Ellis (47) in 1957 described a patient with massive liver metastases from a carcinoid tumor of the rectum, who remained well for the next year and a half after 80 milligrams of HN_2 were injected into the hepatic artery. The best results were achieved in Kaposi's sarcoma; Cook (35) in 1959 reported no recurrences after 3 months to 2 years in 5 out of 21 patients. Whereas some investigators express more optimistic views, Grady, Krantz, and Brown (58) stated after their experience with intermittent injections of HN_2 via cannulated arteries, ". . . the occasional palliation obtained does not warrant the time consuming and vigorous procedure, symptomatology accompanying therapy and the attendant complications." Boiman, Holzaepfel, and Barnes (18) and Bonner, Thurman, and Homburger (19) came to the same conclusion.

The article of Sullivan, Miller, and Sykes (127) deserves special mention because these investigators were the first to test clinically the suggestion of Klopp and his colleagues (76) to use an antagonist to decrease the systemic toxicity. For this purpose, intramuscular injections of citrovorum factor were given to counteract the toxic systemic effects of the methotrexate, which was used as the chemotherapeutic agent. A course of therapy consisted of continuous intra-arterial infusion of methotrexate, usually 50 milligrams per 24 hours, for 6 to 10 days, during which time citrovorum factor was given intramuscularly at varying intervals in a dose of 3 to 9 milligrams every 4 to 6 hours. Eighteen patients were treated and tumor regression was noted in 10. Three of the 18 patients could not be evaluated for antitumor effects because the catheters were not positioned accurately. In 5 patients response could not be determined, either because of the site and extent of the tumor or because the early death of the patient resulted in an inadequate trial. Recently, Sullivan and his as-

TABLE III.—INTRA-ARTERIAL INJECTION

Author	Year	Agent	Dosage, mgm.	Time	Tumor	Improved/total patients: Brain	Head and neck	Extrem.	Pelvis	Liver	Skin	Other	Total
Klopp *et al.* (76).....	1950	HN_2	10–122	6–22 days		2/2	7/7	1/1					10/10
Barberio *et al.* (10)...	1951	HN_2	88	16 days									
			64	64 days					2/2				2/2
Bateman *et al.* (13)...	1951	HN_2	11–155	5–18 days									?/22
Bierman *et al.* (16)...	1951	HN_2	5–80	Single dose	Mycos.* fungoid.						?/17		?/17
Bonner *et al.* (19)....	1952	HN_2	5–88	2–69 days	Inoper. Ca	1/3	2/7	1/1	2/3			1/2	7/16
Cromer *et al.* (39)....	1952	HN_2	24–100	6–15 days					14/16				14/16
Albertelli *et al.* (3) ...	1953	HN_2	70–90 t.d.						8/21				8/21
Barberio *et al.* (9)....	1953	HN_2+ aureomycin	dosage tolerance		Inoper. Ca				10/14		1/1	2/2	13/17
Grady *et al.* (58).....	1953	HN_2		Intermitt.	Advanc. malign.								3/11
Sullivan *et al.* (126)	1953	HN_2	20–155 t.d.		Incur. neopl.								8/14
Boiman *et al.* (18)....	1956	HN_2	0.89–1.09/ kgm.	1–2 ×	Cer., fund., ovary				?/20				?/20
Ellis (47).....	1957	HN_2	80	1 day	Carcinoid rectum					1/1			1/1
Ultman *et al.* (131)...	1957	TSPA	5, 10										?/2
Davis and Shumway (44).....	1958	HN_2(2)† TSPA			Met. brain tumor	14/14							14/14
Krakoff and Sullivan (78)	1958	HN_2'	0.4/ kgm.	1×	Pelvic Ca				18/29				18/29
Reese *et al.* (104)....	1958	TEM +rad.	1.5–2	1 day			2/2						2/2
Shiraha *et al.* (117)...	1958	Mitomycin C	3–156	2–82 days									7/18
Cook (35).....	1959	HN_2‡	0.4/ kgm.		Kaposi sarcoma			14/21					14/21
Malm *et al.* (86).....	1959	HN_2 etc.				?/1	?/3	2/6	2/13			?/1	?/23
Sullivan *et al.* (127)..	1959	Methotrexate	50/ 24 hr	6–10 days	Incurable cancer								10/18
Sullivan *et al.* (128)..	1960	Methotrexate	50/ 24 hr	6–10 days	Ca Cer., uterus								5/5
Totals.....						17/19	11/16	18/29	56/98	1/1	1/1	3/4	136/215
Per cent.....						89	69	62	57	100	100	75	63

*Prompt response 3 out of 4.
†Two patients treated in 1943, 1951.
‡Three patients had combined intra-arterial and intravenous therapy.

sociates (128) applied the same technique in the treatment of cancer of the cervix in Kenya, Africa, where radiation therapy is not available. Total or partial tumor regression and clinical benefit were reported in all patients. One of these patients showed no clinical evidence of residual cancer in the cervix, vagina, or pelvis 29 days after onset of therapy, and a posttreatment biopsy specimen was free of tumor.

In evaluating the possibilities for intra-arterial injection, it should be compared with localized external roentgenotherapy. In our opinion, the results reported with intra-arterial chemotherapy are not better than those reported with good radiation therapy. Improvements similar to those reported for the intra-arterial injections can easily be accomplished with palliative radiation therapy. Long term control by radiation therapy is frequent in carcinoid tumors because of their slow growth rate and in Kaposi's sarcomas because of their high radiosensitivity. More than 50 per cent of all patients with carcinoma of the cervix can be cured with good radiation management. Unfortunately, workers in the chemotherapy field often have little experience with the effectiveness of roent-

genotherapy. The fact that the roentgenotherapy cure rate for most tumors is not high is often misinterpreted to mean that this modality is not effective in accomplishing regression. From a theoretical viewpoint, intra-arterial injection appears inferior to external roentgenotherapy in the following respects: (1) Proper localization of the effect is rarely possible because tumor growth does not follow the arterial distribution, whereas with proper roentgenotherapeutic techniques good localization can usually be achieved; (2) dosimetry with intra-arterial injections is uncertain whereas radiation dosimetry is highly developed; (3) systemic effects cannot be as readily avoided with intra-arterial injections as with localized roentgenotherapy; and (4) the time of administration cannot be as easily varied with intra-arterial injection as with roentgenotherapy to fit the special situation. This picture could of course change radically if a chemotherapeutic agent were found which is strikingly more effective than radiation.

A suitable application for intra-arterial injection, even with the presently used agents, might be its use as an adjunct to operation for the same conditions in which preoperative and postoperative radiation therapy are currently employed. Preoperative and postoperative radiation therapy is usually given in moderate doses and to rather large fields in order to inactivate small cancer deposits which are not excised. Intra-arterial injection for this purpose could be carried out at the time of operation and would be greatly facilitated by the surgical findings, the visualization of the tumor spread, and the surgical exposure of the vessels. Exact localization is in this case not as essential as in the treatment of gross tumor.

Perfusion. Intravascular perfusion is the logical development of intra-arterial injection because with this method the effects of the chemotherapeutic agent can be localized to the region of the tumor. Perfusion thus makes it possible to use chemotherapeutic agents which are not fixed rapidly or do not act quickly.

Perfusion with chemotherapeutic agents was first suggested by Klopp and his co-workers (76) in their report on intra-arterial injection in 1950. Its experimental and clinical use was pioneered by Creech and his associates (37, 38), who treated their first patient in June 1957 and by December 1959 had reported their experience in many articles. They use a pump-oxygenator circuit for perfusion, consisting of a sigmamotor pump and a bubble oxygenator. With the sigmamotor pump, perfusing pressures can be maintained which approach systemic arterial pressure. With the bubble oxygenator, an oxygen tension of 600 to 700 millimeters is reached, which is much higher than that usually present in the arterial blood, 150 millimeters.

Creech and his co-workers express the hope that the increased oxygen tension in the blood will increase the differential effect on the tumor cells, as first suggested by Gray, Conger, Ebert, Hornsey, and Scott (61) in 1953. From Gray's experimental work and the clinical reports of Churchill-Davidson, Sanger, and Thomlinson (30, 31) and Sanger (107), it appears doubtful that the increased oxygen tension produced by the bubble oxygenator in a perfusion circuit is sufficient for a worthwhile effect. Churchill-Davidson is now using an oxygen pressure of three or four atmospheres. This necessitates a complicated procedure involving the use of a pressure chamber, myringotomy, and general anesthesia. On the other hand, some reports have appeared in the literature which might indicate that simple inhalation of oxygen is worth while, including those of Hultborn and Forssberg (69) and Saal and Dalicho (106).

Creech and his associates have used HN_2, TSPA, PAM, 5-FU, and Act.-D in their studies. HN_2 and 5-FU are given in 4 equal doses 5 minutes apart and perfusion is continued for a total of 30 minutes. PAS and TSPA are administered in 2 equal doses 5 to 10 minutes apart; the entire period of perfusion is 45 to 60 minutes. PAM and TSPA are longer acting than HN_2 and 5-FU. Act.-D has a duration of action somewhere between these two groups and is administered in 2 to 3 doses about 10 minutes apart. To remove residual TSPA and PAM, the venous system is drained of blood and the extremity irrigated with 500 cubic centimeters of dextran, which is administered through the arterial cannula and drained by the venous line. In other areas, such as the pelvis, exsanguination is not feasible; therefore, 600 to 700 cubic centimeters of blood are removed and irrigation with dextran is carried out.

Table IV summarizes the perfusion techniques and the doses of various agents which Creech and his associates recommend on the basis of their experience. These doses are higher than those ordinarily used for systemic treat-

TABLE IV.—TECHNIQUES FOR PERFUSION DEVELOPED BY CREECH AND ASSOCIATES

Perfused region	*Circuit*	*Tourniquets*	*Recommended dose, mgm./kgm.*				
			HN_2	*TSPA*	*PAM*	*5-FU*	*Act.-D*
Lower extremity	Common femoral A and V or external iliac A and V	Above level of cannulation	0.8	1.0	1.5	20	0.05
Upper extremity	Brachial A and V or axillary A and V	Through axilla over shoulder	0.6	0.8	1.5	15	0.035
Pelvis	Abd. aorta and inf. v. cava with proximal occlusion* by balloons	Upper thighs	1.0	1.0	2.0	20	0.05
Lungs	Pulmonary circuit; left atrium to pulmonary A and heart-lung bypass, v. cava and femoral A†						
Breast	Subclavian A and V	Arm					

*Below renal branches.
†Pump oxygenator used.

ment. Since in most cases the perfused volume is in the order of 10 per cent of the volume of the whole body, the concentration of the chemotherapeutic agent in the tumor area is 15 to 20 times greater than that resulting from systemic administration.

In their first 73 patients treated by the perfusion method, HN_2 was used in 38 patients, TSPA in 4, PAM in 24, 5-FU in 1, Act.-D in 6, and Chlorpactin XCB in 1. In 1 patient combined therapy with TSPA and PAM was carried out. Four patients were perfused twice; 1 patient was perfused three times.

A brief analysis of the results of perfusion in these 73 patients as reported by Creech and associates in May 1959 is given. For the assessment of benefits, the 17 cases in which therapy was classified as "adjuvant" were omitted, since they do not permit one to judge the effectiveness of the method.

Of the 37 carcinomas, 9 involved the breast, 7 the rectum and colon, 7 the lung, 11 the genitourinary system, and 1 each the liver, the thumb, and the oropharynx. HN_2 was employed in 28 cases, TSPA in 3, Act.-D in 5, and chlorpactin in 1 case. Four operative deaths occurred in this group, a mortality of 11 per cent. Of the 28 patients receiving palliative therapy, 12 or 43 per cent are reported as showing significant response to perfusion.

Of the 18 sarcomas, 4 were osteogenic sarcomas, 3 rhabdomyosarcomas, 3 liposarcomas, 2 lymphosarcomas, and 6 were other soft tissue lesions. They were located in the lower extremity in 9 cases and in the upper extremity in 7. In 2 cases the tumors were disseminated. HN_2 was employed in 10 cases, PAM in 6, 5-FU in 1, and Act.-D in 1. No operative death occurred in this series. Perfusion was performed twice in a case of chrondrosarcoma with good response of the tumor in each instance. In osteogenic sarcomas, response to perfusion was slight. Of the 14 patients receiving palliative therapy, 4 or 29 per cent are reported as showing significant response to perfusion.

PAM was used in the 18 cases of melanoma. One of these patients also received TSPA. There was 1 operative death, a mortality of 6 per cent. Of the 14 patients receiving palliative therapy, 7 or 50 per cent showed a significant response to treatment.

Complications of the isolation-perfusion technique consisted of edema and skin changes in the perfused area. Edema occurred after perfusion of an extremity in 10 cases. It responded to the usual management. The most troublesome complication appeared when regional node dissection was combined with perfusion. In 2 of these cases necrosis and delayed healing of the skin flaps were observed. In some cases when high concentration of a chemotherapeutic agent was employed in perfusing an extremity, erythema appeared almost immediately and edema within 24 to 48 hours after perfusion. During the first 7 to 10 days, pigmentation of the skin developed, which faded gradually. Gastrointestinal symptoms were usually mild and transient. Nausea and vomiting were not more frequent than that occurring after general anesthesia.

The blood count was only moderately depressed. In 38 cases, or 52 per cent, there was no significant reduction of the peripheral leukocyte count, whereas in 15, 20 per cent, depression of 75 to 100 per cent was present. In 1 patient with malignant melanoma, in whom the entire right lower extremity and pelvis was involved, 3 milligrams per kilogram of PAM were used. About the eighth day severe depression of hematopoiesis appeared and the patient died of septicemia on the fifteenth day.

In their latest article (38), the same investigators report the results of perfusion in 120 patients, including 59 with carcinoma, 34 with melanoma, 25 with sarcoma, and 2 with glioblastoma. A total of 145 patients with cancer were treated by perfusion methods but 25 were treated too recently to be included in evaluation of results. Results were similar to those reported for the early series. The authors comment: ". . . in no instance has the response to a neoplasm been indicative of true specificity" (of the chemotherapeutic agent) and ". . . that there is little specificity of an agent for a given tumor."

Reports of Malm, Herter, Frick, Long, and Demetz (86), of Stehlin and his co-workers (123), and of Jesse (71) corroborate the findings of the Creech group. Hickey, Johnson, Evans, and Alftine (66) used a combination of HN_2 and radiocolloids for perfusion in the treatment of 5 patients with lesions involving the extremities and 3 benefited. Ausman and Aust (6) in 1959 attempted perfusion of the liver with HN_2 in 4 patients. Woodhall, Hall, Mahaley, and Jackson (139) have carried out perfusion of the brain in 4 patients.

The studies of Stehlin and his co-workers (122) have shown that the leakage factor in regional perfusion with chemotherapeutic agents is high for most locations. Based on calculations at the end of 1 hour, they found that the leakage factor for popliteal perfusion was 5 per cent, for iliac and femoral perfusion 20 per cent, for pelvic perfusion 50 to 75 per cent, for external carotid perfusion 80 per cent, and for axillary perfusion 94 per cent.

The reports show that regression of tumors which do not respond to a systemic administration of chemotherapeutic agents can be accomplished with perfusion techniques. However, we doubt that the results achieved today by perfusion surpass the accomplishments of good local radiation therapy as is claimed by Creech and associates for melanoma, which is usually labeled "radioresistant." Many melanomas show good regression to radiation therapy, and we have seen many worthwhile palliative results. We believe that a controlled clinical study is required before a claim of superior results with perfusion in melanoma can be accepted.

In evaluating the future possibilities of perfusion, one should remember that it must be considered as a modification of intra-arterial injection. Perfusion has the advantage that the chemotherapeutic agent is to a much higher degree excluded from the general circulation, but the disadvantage that the technique is much more involved. Perfusion, like intra-arterial injection, is suitable only for treating relatively large volumes and thus competes with localized large-field roentgenotherapy. Therefore, the same considerations apply as given in the discussion of intra-arterial injection versus localized roentgenotherapy. For these reasons, we believe that with the present chemotherapeutic agents, intravascular perfusion should not be recommended except for carefully controlled clinical studies. These may provide valuable information on the mechanism of action of chemotherapeutic agents as well as on the metabolism of tumors.

INTERSTITIAL APPLICATION

The interstitial application of chemotherapeutic agents will be divided for this discussion into: (a) interstitial injection and (b) interstitial implantation.

Interstitial injection. Interstitial injection in this review of local cancer therapy is defined as the injection of drugs in fluid carriers into and around tumors. We prefer the term "interstitial injection" to the term "intratumoral injection" because it often may appear desirable, as in radiation therapy, to "cover" not only the tumor but also the surrounding tissue.

Interstitial injection of modern cancer drugs dates back to 1931, when Adair and Bagg, at the Memorial Center, injected a mustard gas solution into a recurrent neurogenic sarcoma of a 48 year old patient. They reported that ". . . a terrific reaction resulted but a neurogenic sarcoma several times recurrent has practically disappeared following this violent therapeutic reaction . . ." This report appeared more than 10 years before nitrogen mustard was tried for systemic cancer therapy.

Many reports on newer chemotherapeutic agents contain descriptions of interstitial injections. Those found in the literature through June 1959, listed chronologically in Table V, will be discussed briefly.

Bateman stated in 1955, "After several trials with local injection, it became apparent not only that a larger single dose could be employed thereby, but also that, in addition to greater local effect, distant disease was likewise affected." TSPA was used in 34 patients with far-advanced

TABLE V.—INTERSTITIAL INJECTION

Author	*Year*	*Agent*	*Dosage*	*Time*	*Tumor*	*Improved/ total pts.*
Adair and Bagg (2)	1931	Mustard-gas solution	3 minims	1 day	Recurrent neurogenic sarcoma, rt. thigh	1/1
Bateman (11)	1955	TSPA	5–40 mgm.	weekly	Ca ovary, cervix, GU system, lung, CNS	18/20
Shay and Sun (114)	1955	TSPA	11 mgm. (total dose)	24 days	Subcutaneous tumor nodules	2/2
Bucher (25)	1958	Ethylene-imine quinone, E 39	20–30 mgm.	6–14 ×	Bladder	?/7
Wright *et al.* (141)	1957	TSPA	10–40 mgm. 1–5 ×	1–318 days	Melanoma (1), breast (1)	2/8
Bateman (12)	1958	TSPA ODEPA	3–60 mgm. 3–80 mgm.	1–4 week intervals	Advanced breast cancer	89/140
Conway and Griffith (34)	1958	TSPA	35 mgm., t.d.	23 days	Malignant melanoma	1/1
Davis and Shumway (44)	1958	TSPA			Local skin metastases	
Schell and Hall (110)	1958	TSPA TEM	40–100 mgm. single ds.		Ca kidney, cystadenoma of ovary, melanoma	
Shiraha *et al.* (117)	1958	Mitomycin C	21–84 mgm.* total ds.	29–56 days		4/4
Mrazek *et al.* (95)	1959	TSPA	10–20 mgm.	daily		
Wright *et al.* (140)	1959	TSPA	5–40 mgm. single dose	weekly interval	Disseminated breast cancer	5/11†
Total						122/187
Per cent						65

*Combined with intravenous administration of mitomycin C.
†Of the 11 patients, 10 also received drug intramuscularly; however, improvement was noted mainly after interstitial injection.

mammary carcinoma. Best results were achieved with local injection, 26 patients. In 12 patients with ovarian carcinoma, TSPA was injected directly into tumor tissue, through the vagina in 10 patients, and into residual tumor at laparotomy in 2. Palpable pelvic masses completely disappeared in 3 patients, and the size of the tumors decreased in 8 others. One patient with adenocarcinoma of the endocervix was given 2 injections of TSPA into a large, fungating tumor before hysterectomy. Grossly, the lesion appeared to shrink and disintegrate. Side effects after treatment were rare. However, the limiting factor was hematopoietic depression. Cessation of treatment was usually followed by recurrence or progression of disease. Maintenance therapy was accomplished by injection of the drug at intervals of 1 to 3 weeks. Bateman also states that her experience with local injection of TSPA into tumors of the urinary tract has been encouraging.

Shay and Sun (114) treated 2 patients with subcutaneous tumor nodules by local injections of TSPA. The intravenous administration of TSPA had produced a satisfactory response in these patients in other tumor sites but had failed in four skin nodules. Local treatment of the nodules produced complete disappearance of cancer cells in 1 case and changes in the cellular structure in the other.

Schell and Hall (110) used TSPA locally in several cases. Hyaluronidase was employed as a spreading agent, and in some instances epinephrine was employed to produce vasoconstriction and delay systemic absorption. Occasionally TEM was given by direct injection into tumor masses. In 1 patient with cystadenocarcinoma of the ovary, 10 milligrams of TEM and 150 units of hyaluronidase were injected into a large pelvic mass with concomitant systemic use of TSPA. The patient died 6 weeks later. At autopsy, no viable tumor could be found in the pelvis and the previously solid pelvic mass was converted to a fibrous shell, filled with hemorrhagic necrotic debris. One patient with malignant melanoma showed transient improvement after direct injection of TSPA into several painful nodules.

Wright and his associates (141) describe 1 case of a patient with malignant melanoma who had 11 subcutaneous nodules, ascites, obstipation, and vomiting. Forty milligrams of TSPA were injected into the largest nodule. Twenty-four hours later the nodule was half its original size. Four days later the nodule was again injected with 20 milligrams TSPA, and the same dose was repeated on the eighth day. Ten days after the institution of treatment, all of the subcutaneous nodules had disappeared. Wright's group (140) also observed tumor regression in 5

of 11 patients with disseminated breast cancer treated by direct injection of TSPA.

Bateman (12) in 1958 stated that no improvement was noted in any patient with hepatic metastasis from breast carcinoma who was treated with TSPA until the drug was injected intrahepatically. Of a total of 140 patients with advanced breast cancer treated by local injection of TSPA or ODEPA, 89 showed improvement. Shiraha, Sakai, and Teranaka (117) used mitomycin C intravenously in combination with direct tumor injection in 4 patients. They reported softening and necrosis of the tumors, but all of the patients died after total use of 29 to 56 milligrams of mitomycin C.

Combining all studies, there is a total of 187 cases for which results have been reported including treatment with mustard gas solution. TSPA, ODEPA, E 39, mitomycin C, and TEM in varying doses. It is claimed that 122 patients, 65 per cent, have benefited from this procedure. Nearly all observers state that better tumor regression was obtained with interstitial than with systemic applications. Little attention is paid to the problem of proper distribution and dose, however. In this respect, the status of interstitial injection is similar to that of radiation therapy in its first decade, when radiation in uncertain distribution and unknown amounts was given. Tumor regression was usually accomplished, but the results were unpredictable, permanent cures rare, and complications frequent. Only after distribution and dose were controlled within narrow limits did radiation therapy become of real value in cancer management. The underlying reason for this is that the differential between cancerous and normal tissue is not great enough to permit inaccurate application of any agent, be it radiation or drug.

Since interstitial injection of drugs appeared to us as a sound method in principle, we have made many attempts to improve this technique over the past years. Our earliest attempts were patterned after a technique developed by us for the implantation of radioactive sources: Hollow needles were first inserted in the tumor at 1 centimeter intervals. Next, a graduated syringe was attached to each needle in turn and while the needle was slowly withdrawn, a certain amount of fluid per needle length was injected. With this method, the distribution was better, but was still not satisfactory because the resorption of the injected fluid was too variable. In addition, the injected solution tended to leak out along the needle track and damage the skin.

For the evaluation of the possibilities of interstitial injection of chemotherapeutic drugs, a short review of the experience with interstitial injection of radioactive isotopes appears useful. The injection of radioisotopes affords the unique opportunity of studying the distribution of the material in tissue by assaying the radioactivity in various areas.

The earliest work in this field was reported by Müller (96) in 1945. Müller initially used interstitial injection of a semicolloidal radioactive zinc suspension in a small group of patients with stage III carcinoma of the cervix. Subsequently, Flocks, Kerr, Elkins, and Culp (52) at the University of Iowa used injections of radioactive colloidal gold for the treatment of carcinoma of the prostate and Allen, Sherman, and Camel (5) in St. Louis used injections of radioactive colloidal gold into the parametrium supplementary to the usual radium treatment of cervical cancer.

Flocks, Culp, and Elkins (50, 51) as well as Allen, Sherman, and Camel (5) have published optimistic reports on the value of this interstitial injection of radioactive colloidal gold. However, a number of recent investigations have pointed to some serious shortcomings of the injection method. Kerr, MacDonald, Smythe, and Comet (75), for instance, found in studies with 72 dogs that after injection of radiogold into the prostate, large and unpredictable amounts escape into the blood stream in the first few minutes, into the urine in the first few hours, and into the lymphatics in the first few days, leaving only a fraction varying between 0.2 and 4.0 per cent of the injected material in the prostatic tissues. This capricious variability in delivered dose was confirmed by a study of human prostates removed for benign hypertrophy after the interstitial injection of radiogold. Kerr and his coworkers concluded that the interstitial injection of radiogold would not be suitable for definitive treatment of prostatic carcinoma. In another report Hinman and Sheline (67) demonstrated by radioautographs and microscopic sections that the distribution of radioactive gold and chromic phosphate is not even throughout the prostate. They also believe that the rather severe reactions, such as local edema, rectal complications, and intractable pain, occur frequently enough to leave doubt as to whether the

patients are really better off as a result of the isotope therapy.

In a necropsy study, Orr, Thomley, and Campbell (100) found that some portions of the prostate showed six times as much activity as adjacent areas and that viable cancer cells remained. They also found more of the injected radiogold in the liver, spleen, and bone marrow than in the prostate. Similarly, Bulkley and O'Conor (26) present the following conclusion: "A review of experimental studies after injection of radioactive gold, Au^{198}, into the canine prostate shows that it is impossible to irradiate the gland completely because of poor distribution of the colloidal solution. After injection into the dog's prostate, loss of injected radioactive material into the bladder and urethra, as well as into the blood stream, and, thence, to distant organs, leaves about 10 per cent of the total injected dose acting directly on the prostate. A comparable percentage seems likely in human subjects, according to the figures of blood and urine losses in patients after injection of Au^{198} into the carcinomatous prostate. The progress of a group of 40 patients receiving Au^{198} intraprostatically was carefully followed. Only 7 of this group seemed to obtain significant palliative effects from irradiation. Complete control of carcinoma of the prostate by this method of treatment seems highly improbable."

The hope that injected radioisotopes would sterilize cancer in the lymph nodes has also not been fulfilled. Thomas (129), for example, in a study of the lymphatic dissemination of radiogold in the presence of lymph node metastases found that of 593 lymph nodes examined, 94 contained cancer and in only 33 of these, or 35 per cent, was radioactive gold deposited. Of 499 nodes free of cancer, 340, or 70 per cent, contained radioactive gold. Thomas concluded that the uptake of the radioactive colloid in nodes with metastatic cancer is so uncertain that an attempt to treat patients in this manner might possibly be hazardous, because of the dissemination of the radioactive material to unpredictable sites.

Interstitial implantation. The term "interstitial implantation" is used for the interstitial application of chemotherapeutic agents in solid or semisolid form. We have developed a method for this type of application with the intention to achieve better distribution and dosimetry than possible by interstitial injection (65).

The chemotherapeutic agent, nitrogen mustard, is dissolved in a vehicle, carbowax. The mixture is aspirated into 20 gauge stainless steel needles, each 15 centimeters long. These are placed in a horizontal position, and the mixture solidifies while cooling. The whole procedure is carried out under sterile precautions and the loaded needles are stored together with stylets in sterile envelopes. They are thus ready for use at any time.

The needles are implanted in and around the tumor, about 1 centimeter apart from each other. After a satisfactory pattern has been accomplished, the needles are retracted over a stylet, which is fixed with a calibrated instrument against the skin. This leaves along the needle tract a cylinder of the mixture from which the chemotherapeutic agent diffuses into the surrounding tissue. Thus, a well defined amount of the chemotherapeutic agent can be introduced per cubic centimeter of tissue. The technique is similar to the one we have developed for the accurate implantation of radioisotope sources.

Such implants produce reactions similar to those induced by local irradiation. Like radiation reactions, they are limited to the implanted area. If high concentrations of the chemotherapeutic agents are used, ulcerations develop, which resemble radiation ulcers in their course and appearance. They provide a good basis for determining tolerance limits.

The effectiveness of such chemotherapy implants can be nicely demonstrated in experiments in mice with sarcoma 180 transplanted to both flanks. After the tumors on each side have reached an equal size of about 1 centimeter diameter, one is implanted with the mixture of the chemotherapeutic agent and carbowax. The tumor on the other side is used as a control; either it is implanted with carbowax only or it is not implanted at all. With effective agents, the implanted nodule may regress completely, while the tumor on the other side continues to grow. This shows clearly the localization of the chemotherapeutic effect.

Since June 1959, we have cautiously used our method in 4 patients with advanced cancer. The best response was obtained in a patient with metastatic oat-cell carcinoma of the lung. Upon exploration of the chest 6 months previously, an unresectable, oat-cell carcinoma of the lung was found. The patient subsequently received roent-

genotherapy with a 5,200 roentgen tissue dose in 5 weeks. After this treatment, his primary tumor remained under control, but 5 metastatic nodules developed in the thoracotomy scar as well as in the left supraclavicular area. Two nodules were implanted with the HN_2-carbowax mixture in two different concentrations. One nodule was injected with HN_2 in saline. The nodule in the supraclavicular area was implanted with a removable implant of iridium 192, which delivered a tumor dose of 6,000 roentgens in 6 days. The fifth nodule, used as a control, was implanted with carbowax only. The best regression occurred in the nodules implanted with HN_2 in carbowax and with iridium 192, while no regression took place in the control nodule. However, the nodules implanted with HN_2 in carbowax recurred and within 2 months were their original size. From this and the experience in our other patients, we estimate that the effect of the mixture which we used in most implants—6 per cent HN_2 in carbowax = 1.5 milligram HN_2 per centimeter in a 20 gauge needle—is comparable to a radiation dose of approximately 1,000 roentgens. Only a slight erythema was observed with these doses, but no late skin reaction. This indicates that it might be possible to increase the amounts of agent. However, in 1 patient with a large metastasis in the neck from a squamous cell carcinoma of the larynx, a marked temporary swelling was observed. Thus caution is called for in using higher doses. The swelling may have been due to the short time of action of the HN_2, since its appearance was similar to the reaction after high doses of radiation in a single treatment.

For chemotherapy implants, agents should be considered which are undesirable for systemic chemotherapy because they produce a severe local reaction. The agents developed specifically as vesicants for war purposes were therefore evaluated. On recommendation of the Army Chemical Warfare Center, experiments were started with SM-1, 1,2,-Bis(B-chloroethylthio) ethane, which has the strongest vesicant action known (55). This material has to be handled with great care during its incorporation into carbowax. After it is properly mixed, it appears safe to handle with proper precautions. This agent produces a well localized effect. In animals better tumor regression and less systemic effect was accomplished than with agents used for systemic chemotherapy. Another agent which is currently under study for chemotherapy implants is lewisite. It appears promising because in the British antilewisite (BAL), an effective counter agent for the systemic effects is available.

AGENTS FOR LOCAL CHEMOTHERAPY

The most desirable property of an agent for local chemotherapy is the same as for systemic chemotherapy, namely, a highly selective effect on the tumor cell. Besides this fundamental requirement for any good chemotherapeutic agent, certain properties are of special interest for local chemotherapy. They are: (a) time for inactivation, (b) fixation in tissues, (c) solubility, (d) local reaction and, (e) neutralization by antagonists.

Inactivation. Knowing the time required for inactivation of the chemotherapeutic agent is of interest for local chemotherapy because in all of the application techniques, some of the chemotherapeutic agent escapes into the general circulation. If the agent is inactivated before this leakage occurs, systemic effects are avoided. Agents which are quickly inactivated, therefore, offer advantages for local chemotherapy.

The commonly used chemotherapeutic agents differ widely in this respect. Unfortunately, only a few exploratory studies have been made. One was carried out by Karnofsky, Graef, and Smith (73) in 1948, another by Boone, Rogers, Maxfield, and Storer (21) in 1957. At one end of the scale is HN_2, which in the tissues is converted into an inactive form in a few minutes. At the other end are amethopterin and aminopterin, which are believed to be present in the tissues chemically unchanged for several weeks after administration. Most alkylating agents, such as TEM, TEPA, and TSPA, are inactivated in a short time, although not quite as rapidly as HN_2. 5-FUDR and 6-MP have a longer time of action than this group. Act.-D appears to be inactivated quickly.

Fixation in tissues. Fixation of the agent in tissues is of interest for local chemotherapy because it may offer another way to avoid systemic effects of an agent.

Various possibilities exist for fixation of an agent in the tissue. The particle size can be made so large that the agent does not pass into the blood stream. This is utilized in the intracavitary and interstitial injection of radioactive colloids, such as radioactive gold, Au^{198}, and

radioactive phosphorus, P^{32}. Or the agent can form a complex with the tissue proteins. This is an interesting property of the rare earths and is utilized in the intracavitary and interstitial injection of radioactive yttrium chloride, Y^{90}.

For systemic chemotherapy, fixation in tissues appears undesirable because it would impair the uniform distribution of the agent and would produce local reaction at the injection site. No attempts have been made, to our knowledge, to develop chemotherapeutic agents which become fixed in tissues, and no information is available on the degree of fixation of the common chemotherapeutic agents in tissues. However, in the search for better agents for local chemotherapy, fixation in tissues appears as an important consideration.

Solubility. Solubility of chemotherapeutic agents is of interest for local application because poor solubility may prevent leakage of the agent into the circulation, thereby avoiding undesirable systemic effects. For systemic chemotherapy, in contrast, good solubility is desirable to accomplish even distribution. Accurate data are available on the solubility of all important chemotherapeutic agents.

HN_2, TEM, TEPA, and TSPA are readily soluble in water. 5-FUDR and Act.-D are fairly soluble. Amethopterin, aminopterin, chlorambucil, and 6-MP are acids which are insoluble. However, if neutralized first to the sodium salt, they are readily soluble in water. Myleran is insoluble in water.

No studies have been made, to our knowledge, of agents with low solubility for local chemotherapy, but such agents provide another avenue toward enhancing the local effect while decreasing the systemic effect.

Local reaction. Local reaction in the form of inflammation and ulceration may be caused by one or several of the previously discussed properties, or it may be caused by the presence of chemical groups which produce a vehement tissue reaction. An agent with a strong local reaction is in principle undesirable for systemic chemotherapy, because it may produce tissue necrosis and vein thrombosis at the injection site. Such an agent would also be undesirable for oral use. However, some of the most useful chemotherapeutic agents fall into this group.

Of the commonly used chemotherapeutic agents, the strongest locally effective compounds are Act.-D, HN_2, and hemisulfur mustard. 6-MP has an intermediate local effect, while TEM, TEPA, TSPA, nitromin, and 5-FUDR produce only weak local reactions if any.

Since a severe local reaction is not necessarily objectionable in local chemotherapy, it appears worth while to review the list of agents which have been rejected for systemic therapy because of this property and to determine whether any of them are suitable for local chemotherapy. A ready-made collection of such agents is found in the vesicant compounds for chemical warfare. The best known are mustard gas, lewisite, and SM-1. They are potent in the vapor and in the liquid phase. They rapidly penetrate the skin and injure all tissues with which they come in contact. They react readily with nucleoproteins and nucleic acid causing heritable mutations, affecting chromosome structure, and inhibiting mitosis. They have a strong inhibitory action on the pyruvate oxidase system by combining with an SH group, according to Cullumbine (40). Our preliminary studies discussed previously seem to indicate that these agents offer good possibilities for local chemotherapy, at least in the implantation methods.

Neutralization by antagonists. Whereas neutralization by antagonists assumes little importance for systemic chemotherapy, it is of cardinal interest for local chemotherapy because of the possibility of counteracting systemic effects even with considerable leakage of the agent into the circulation.

Antagonists to HN_2 have been investigated most carefully. Considerable work has been done in this field, because the same agents are used to counteract radiation effects. Most studies have been carried out with antagonists to alkylating agents: Cysteine as an antagonist to HN_2 has been studied by Weisberger and Heinle (133); Weisberger, Heinle, and Levine (134); and Brandt and Griffin (23). AET as an antagonist to HN_2 has been investigated by Kelly, O'Gara, Rall, and Zubrod (74) and by Rall, Kelly, O'Gara, Shnider, and Zubrod (103). Its value as a systemic antagonist for intracavitary injection of HN_2 has been demonstrated by Back and Ambrus (8). AET was also found to be an effective antagonist to TSPA by DiPaolo and Moore (45). Unfortunately, AET is too toxic for human use, according to a study made by Condit and his co-workers (33). Other reported antagonists are glucuronic acid for 8-azaguanine and nitromin derivatives,

suggested by Kurokawa (81), and adenine for DON, suggested by Magill and his co-workers (85).

The antimetabolites also appear to be well suited as neutralizing agents. The best studied effect is the neutralization of methotrexate by the citrovorum factor (57). As discussed previously, this effect is being utilized by Sullivan and co-workers in order to deliver high doses by way of intra-arterial infusions.

An important antagonist to lewisite is 2:3 - dimercapto-propanol, named BAL, the British antilewisite. It forms stable ring compounds and in this form the arsenic is relatively nontoxic and does not inhibit the pyruvate oxidase system (101) and other enzymes (46). BAL not only reverses the toxic action of lewisite on the pyruvate oxidase system but also prevents it. The neutralization of lewisite by BAL is very effective and well documented clinically. An improved, nontoxic derivative of BAL suitable for intravenous injection has also been described by Danielli and his associates (43) and by Cullumbine (40). The development of this antagonist makes lewisite a promising agent for local chemotherapy.

SUMMARY

1. For the local treatment of superficial tumors, modern chemotherapeutic agents should be effective. They will not contribute much to practical management of superficial tumors because these tumors are so effectively treated by operation or radiation therapy. However, they may find a place in the management of multiple, small skin cancers, accessible mucosal cancers, and precancerous lesions.

For the treatment of malignant effusions, chemotherapeutic agents appear promising because they are less expensive than radioactive colloids and do not present problems in storage, supply, licensing, and radiation safety. However, more insight should be gained on their mode of action and on their side reactions before they are promoted for general use, especially for intraperitoneal injections.

For the prevention of local recurrences, chemotherapeutic agents appear suitable, but more experimental work on drugs, doses, and application techniques as well as controlled clinical studies are necessary before they can be recommended for routine use in cancer operations.

2. Local chemotherapy by intravenous injections is possible with rapidly deactivated agents. This effect seems to be of importance in the intravenous treatment of lung carcinoma with HN_2. Temporary occlusion of major arteries appears feasible as a means of sparing part of the bone marrow.

Local chemotherapy by intra-arterial injection competes with localized roentgenotherapy. Compared with the present chemotherapeutic agents, roentgenotherapy is superior in our opinion. The most promising use for intra-arterial injection at present appears to be as an adjunct to operation in a manner similar to that of preoperative and postoperative irradiation.

Local chemotherapy by intravascular perfusion is theoretically a sound procedure for treatment of relatively large volumes. The technical difficulties make perfusion less acceptable than intra-arterial injection. With the chemotherapeutic agents presently available, the routine clinical use of perfusion in preference to radiation therapy does not appear justified.

3. Interstitial injection of chemotherapeutic agents is—like the interstitial injection of radioactive colloids—more effective than systemic application and frequently results in good tumor regression, but distribution and dose are too unpredictable for one to achieve consistently good results.

Interstitial implantation of chemotherapeutic agents is worthy of further development. It has distinct advantages over other methods of local cancer therapy: Compared with interstitial injection of chemotherapeutic agents, the results appear more predictable because of the better control of distribution and dose. Compared to perfusion techniques, it is much simpler and the effect can be more accurately limited to the tumor. Compared with external roentgenotherapy, it can be more precisely localized. Compared with interstitial implantation of radium, radon, and radioisotopes, it has the great practical advantage of avoiding all radiation safety problems.

4. Of special interest for local chemotherapy are agents which are quickly inactivated or rapidly fixed in tissues, have low solubility in tissue fluids, cause a strong local reaction, and can be neutralized by antagonists. HN_2 possesses most of these properties. Other agents, such as SM-1 and lewisite, which are considered unsuitable for systemic therapy because of their

severe local reaction, may also be suitable for local chemotherapy.

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ABSTRACTS OF CURRENT LITERATURE

SURGERY OF THE HEAD AND NECK

HEAD AND FACE

Frontobasal Skull Injuries (Die fronto-basale Schaedelverletzung). F. Escher. *Schweiz. med. Wschr.*, 1960, 90: 1481.

Among 180 fractures of the facial bones there were 55 injuries to the frontobasal region, 30 of which presented an open endocranium. In more than half of these 55 cases none or only insignificant signs of a concussion of the brain were noted.

Profuse bleeding is rather uncommon in these cases and may become fatal if the intracranial portion of the internal carotid artery is damaged. Early recognition of shock is vital. Intubation or tracheotomy is often indicated.

The problem of drainage of cerebrospinal fluid is discussed. Early closing of rents in the dura mater is of utmost importance.

Extensive damage to the bony structures may be present and is often difficult to judge from the roentgenograms. Drainage of cerebrospinal fluid is often overlooked, so that meningitis is a common complication. The prognosis when meningitis occurs, however, has much improved. None of 11 patients who had this complication died from the direct consequences of meningitis.

The importance of co-operation of the neurosurgeon, the rhinologist, the oral surgeon, and the ophthalmologist in the care of these patients is stressed. —*O. Erik Hallberg, M.D.*

EYES

The Use of Absorbable Sutures in Surgery of the Cornea. Samuel D. McPherson, Jr. *Am. J. Ophth.*, 1961, 51: 118.

McPherson discusses the use of absorbable sutures in surgery of the cornea. The subject of selection of the most satisfactory suture material for corneal surgery is controversial. Because nonabsorbable sutures have been used routinely the use of absorbable sutures has received but little attention. However, the latter seem to offer a definite advantage in the closure of clear corneal wounds since they need not be removed.

There is a general impression that absorbable sutures may produce unpredictable wound healing and excite more tissue reaction than that caused by silk or other nonabsorbable materials.

The author reports the experimental findings and clinical use of plain and chromic catgut sutures in surgery of the cornea. When the reaction of rabbit's cornea to silk, plain catgut, and medium chromic catgut sutures was evaluated it was found that in 28 days there was little difference in the reaction in clear corneal incisions.

Epithelization of the suture track was found to be as common with catgut sutures as with silk.

Plain and medium chromic catgut sutures used in the closure of clear corneal lacerations in 26 patients did not result in postoperative wound separations or poor wound healing. Suture reaction and corneal scarring were not pronounced subjectively and ocular irritation was moderate.

When used in the direct suture of 2 lamellar and 9 penetrating keratoplasties the absorbable sutures did not produce wound separation or iris prolapse and wound healing was satisfactory. Moreover, corneal scarring and suture reaction were not pronounced. The "disappearance-times" of plain and of chromic catgut sutures from human corneas varied from 5 to 38 days for plain catgut and from 8 to 64 days for chromic catgut.

The author concludes that catgut is a satisfactory suture material and its absorbable quality is an additional advantage over silk.

—*Joshua Zuckerman, M.D.*

Retinal Detachment Surgery. P. Robb McDonald. *Am. J. Ophth.*, 1960, 50: 1247.

This is an analysis of 100 consecutive retinal detachment patients on whom a total of 125 surgical repairs were performed by the author at the Wills Eye Hospital and the Lankenau Hospital in Philadelphia, Pennsylvania. Particular emphasis is placed on the causes of detachment and the causes of failure in treatment with very little attention given to technical minutiae. The median age was represented by 34 patients whose ages were between 60 and 69 years. Two patients who were more than 80 years old were aphakic and both had good results. The 3 patients under 10 years of age were all boys who had sustained trauma some weeks or months previously. A total of 8 detachments could be related to direct trauma, and indirect trauma was probably causative in 3 others. Twenty-three per cent of the series had bilateral detachments, 16 per cent were myopic by more than 3 D., 32 per cent were aphakic, and 15 per cent had had one or two diathermy procedures before referral.

Sixteen patients were treated by intrascleral diathermy alone as a primary procedure with cure in

15; an additional scleroplastic procedure was required in the sixteenth and this resulted in cure. Twenty patients had primary scleral flap procedures without encircling tubes, and 19 were cured by such procedures. Scleroplasty combined with an encircling tube was the author's first procedure in 64 patients and 16 of these required a second procedure. This type of operation was the primary procedure in 30 of the 32 aphakic patients and the secondary procedure in all cases.

Nineteen patients were classified as failures after a total of 32 operations on them. Poor visibility contributed to failure in 5, and myopia of 24 D. in another. Vitreous retraction was believed to be responsible for 5 failures; 4 of these patients had had previous diathermy. Severe uveitis in 2 cases and vitreous hemorrhage in 1 contributed to failure. Technical difficulties at operation were held responsible in 5 patients. Vitreous loss was associated with 3 of the latter cases.

It is urged that diathermy procedures be minimal and be performed under a scleral flap. Late involution of the macula should be watched for since it occurs somewhat more frequently after encircling tube operations. —*Arthur H. Keeney, M.D.*

Use of Intramuscular Chymotrypsin in Controlling Tissue Reaction Following Strabismus Surgery. EDWARD G. FORTIER. *Am. J. Ophth.*, 1961, 51: 106.

FORTIER reports on the use of chymotrypsin intramuscularly in controlling tissue reaction after strabismus surgery. Chymotrypsin minimizes operative reaction in ocular surgery. Five cases are reported in which chymotrypsin was given after strabismus surgery. Two c.c. were injected intramuscularly while the patient was on the operating table or shortly after the patient returned to the recovery room. On the first postoperative day, 1 c.c. of chymotrypsin was given in the morning and this dose was repeated in the afternoon. On the third or fourth postoperative day, 2 c.c. were again administered to some of the patients. It was observed that chymotrypsin was most valuable in the early postirritant phase.

Chymotrypsin in sesame oil is relatively heat stable and requires no special handling other than avoidance of freezing. The newer form of chymotrypsin in aqueous suspension requires temperature control prior to use. It should be maintained at about 40 degrees C. in a refrigerator, but in no case should it be placed in a freezer or should it be allowed to freeze. In the aqueous form both extremely low and high temperatures will detract from its therapeutic efficacy.

Pain at the site of injection may be quite distressing but with proper technique injection can be practically painless. By using a 22 gauge needle, 2 in. in length, it is possible to approximate an intramuscular injection and the likelihood of the drug's following along the path of the needle as it is withdrawn is less likely.

Although postoperative conjunctival injection is not modified nor its duration shortened after treatment with chymotrypsin, postoperative edema after strabismus surgery is definitely reduced. Moreover, patients treated with chymotrypsin experience much less postoperative ocular discomfort and are able to co-operate much better in the early postoperative stages, in this way facilitating examination.

—*Joshua Zuckerman, M.D.*

NECK

Endocrinophoniatric Therapy of the Nodules of the Vocal Cords (Terapéutica endocrinofoniátrica de los nodulos de cuerdas vocales). HORACIO N. GEROSA, ALBERTO BARSA, and ETHEL WELL DE PÍCCOLI. *Sem. méd.*, B. Air., 1960, 67: 1203.

MEDICAL THERAPY of nodules of the vocal cords has consisted of prednisolone per os in two daily doses of 5 mgm. each for a period of 90 days. For incipient lesions the period of administration may be shorter. Then 5 mgm. daily is given for a period of 120 days, followed by 2.5 mgm. daily for an additional 90 days. In instances of surgical ablation of the nodule the medication is continued for as long as 120 days postoperatively, since it is only by this means that recurrence can be prevented. During this period the so-called phoniatric exercises should be carried out; they consist essentially in rest of the intralaryngeal vocal apparatus and proper training of the external or extralaryngeal apparatus, much like the training for professional singers and speakers.

During the first 30 days, as a rule, functional improvement occurs without evident anatomic changes in the lesion. Anatomic changes may be anticipated only after 60 or more days of medical treatment.

As evidence of the correctness of their theoretical considerations the authors point to their experience at the Rawson Hospital, Buenos Aires, Argentina, with 100 cases. Only 87 of these could be followed up for a sufficiently long period to make a definitive evaluation. Evident improvement has resulted from the treatment in all. —*John W. Brennan, M.D.*

SURGERY OF THE NERVOUS SYSTEM

CEREBRUM, CEREBELLUM, AND HYPOTHALAMUS

Therapeutic Application of Certain Radioactive Substances in Neurosurgery (A propos de l'utilisation thérapeutique de certains corps radio-actifs en neurochirurgie). J. P. CONSTANS, G. SZIKLA, and M. DAVID. *Neurochirurgie*, Par., 1960, 6: 113.

THE AUTHORS have used radioactive gold, Au^{198}, intracerebrally on the neurosurgical service of the Hospital de la Pitie, Paris, France since 1952. Au^{198} emits 95 per cent beta rays and 5 per cent gamma rays. In small doses, the gamma effect is negligible; in larger amounts, the adjoining internal capsule may be damaged, in the case of basal ganglia implantations, and the chiasm, in intrahypophysial insertion. Brain swelling several months after implantation has produced the typical findings of a space-occupying lesion, including arteriographic shifts and requiring operative intervention. Ordinary doses of 15 to 20 mc. of Au^{198} produced transitional bands of tissue reaction 10 to 20 mm. thick around the central necrotic areas. This reaction has been corroborated by cat and rabbit experiments. These findings are illustrated by 18 photographs.

The physical properties of radiation from radioactive gold and yttrium, Y^{90}, are compared. The radioactive gold is an effective beta emitter for a distance of 1 to 2 mm. at intensities sufficient to produce necrosis. The beta radiation of yttrium, however, is effective to 3 or 4 mm. This makes Y^{90} a superior agent for producing lesions of the size commonly desired in the hypophysis or basal ganglia. In addition, the yttrium does not emit the noxious gamma radiation which is responsible for the wide transitional band of tissue reaction around the lesions made by gold. The latter effect is desirable in the treatment of gliomas. However, it is not desired in surgical treatment of the hypophysis or basal ganglia. In addition, the authors have found that yttrium produced lesions much more constant in size and shape than those produced by electrocoagulation.

—George L. Potter, M.D.

Report on 456 Hypophysectomies by Means of Electrocoagulation or Radioactive Gold Implantation Through a Percutaneous Paranasal Route (Bericht ueber 456 Hypophysenausschaltungen mittels Elektrokoagulation bzw. Radio-Gold-Implantation auf percutanem, paranasalem Wege). E. KLAR. *Langenbecks Arch. klin. Chir.*, 1960, 294: 497.

OF 82 patients with pituitary tumors treated by percutaneous coagulation or radioactive gold implantation, 47 had good subjective improvement and 27 had good objective improvement. Only 8 had no objective improvement. There were no deaths.

Two hundred and ninety-four patients with breast carcinoma received the same treatment. Most had widespread metastases. Objective improvement was obtained in 15.7 per cent and subjective improvement in an additional 29.0 per cent. All patients with isolated bone lesions improved objectively. Rarely was there improvement of visceral metastases.

Most of 26 patients with malignant melanomas improved subjectively, but only 6 of them had objective regression.

Seven of 12 patients with prostatic carcinoma improved objectively. The acid phosphatase and calcium excretion characteristically returned to normal.

In the entire series, there was only 1 postoperative death. Sixteen patients had temporary diabetes insipidus. In 6 visual field defects developed several months after radioactive gold implantation. There were 10 cerebrospinal fluid fistulas.

—George L. Potter, M.D.

SPINAL CORD

Vertebral Angiomas (Gli angiomi vertebrali). S. TERRACCIANO and A. VITALE. *Rass. internaz. clin. terap.*, 1960, 40: 1028.

FOUR CASES of vertebral angiomas are presented. All 4 were observed in women. Two patients showed only subjective complaints, while in the other 2 signs of compression of the spinal cord were present. In 1 of the latter 2 cases, motor and sensory involvement was present. In this patient, who was only 13 years old, 1.5 months elapsed between the onset of the symptoms and the development of the full-blown picture. In the other case with neurologic manifestations, the course of the disease spread over a period of 18 years. However, a few months from the onset of her complaints the patient received a course of roentgenotherapy with complete relief for about 16 years. Another course given when the symptoms reappeared was ineffective. In these 2 patients laminectomy followed by roentgenotherapy was performed. The 2 patients with only subjective complaints received roentgen treatment alone.

In all cases a complete disappearance of the symptoms was observed up to 6 months after completion of the treatment—the period of the last control. In the 2 patients operated on, histologic diagnosis of benign fibroangioma was made. In 3 of the patients the tumor was located in the low thoracic spine; in the fourth it was located in the lumbar spine.

—Maria Serratto, M.D.

Anterolateral Cordotomy in the Surgical Treatment of Intractable Pain (La cordotomie antéro-latérale dans le traitement chirurgical des douleurs incoercibles). J. BRIHAYE and J. RETIF. *Bull. Soc. Roy. belg. gyn. obst.*, 1960, 30: 481.

EIGHTY-ONE INSTANCES of anterolateral cordotomy are reported, 53 of which were performed high up in the cervical region. The procedure has proved effective in 80 per cent of the patients who were suffering from pain in the lower extremities or abdomen and in 65 per cent of those with thoracic and upper extremity pains. It is believed that, with greater experience on the part of the operator and a better knowledge of the many physiopathologic and surgical as-

pects of the operation of cordotomy, even better results may be procured.

The pain from cancer of the organs of the midline location or with a known bilateral sensory innervation should be treated by a bilateral cordotomy, even though the pains seem to be limited to one side of the body. The motor and sphincter disturbances of the bladder and other portions of the urinary tract are of course well known. The authors emphasize the fact that these disturbances are not very frequently encountered and even with bilateral cordotomy are eventually overcome by the patient.

The total mortality in this series of 81 patients with gynecologic cancer was 8.6 per cent. This mortality was notably higher after primarily bilateral cordotomies.

The authors believe that the cervical cordotomy is to be preferred to the dorsal; its results are noticeably better and its complications are less frequent. Nevertheless, the operative indications should take into consideration the life expectancy of the patient; the operation should not be performed on any patient whose probable survival appears to be very brief. However, such a prognosis is at times difficult to arrive at. Unfortunately, any errors of judgment will influence directly the operative results. In many instances, the referring physician or even the patient herself will demand relief of the pains at any price, and if, under this pressure, the surgeon decides to enlarge the indications which he has established on principle, it is better to operate effectively and at once, before the prognosis is further worsened by attempts at medical antalgic therapy which has been carried to the point where the patient has been reduced to a shadow by toxicomania and advanced cachexia. —*John W. Brennan, M.D.*

PERIPHERAL NERVES

Changes in Nerve Conduction with Ulnar Lesions at the Elbow. R. W. GILLIATT and P. K. THOMAS. *J. Neur. Neurosurg. Psychiat.*, Lond., 1960, 23: 312.

THE AUTHORS have examined the motor nerve conduction and nerve action potentials in the ulnar nerve. Conduction in motor fibers was studied by stimulation just above the wrist and elbow and in the axilla with the muscle response being observed in the abductor digiti minimi or the first dorsal interosseous muscle. Afferent conduction was studied by stimulating the nerve trunk and recording the response at a higher level in the arm.

Fifteen patients were used for a control study and the range of normal values is given. The motor nerve conduction velocity was slightly higher in the forearm-elbow segment when compared to the upper arm.

Fourteen patients with a good clinical diagnosis of an ulnar nerve lesion at the elbow were examined. Thirteen of the 14 showed a substantial reduction in the conduction velocity in the forearm. Slowing distal to the wrist was more variable. In the upper arm a mild degree of slowing was seen. In 9 patients with an ulnar nerve lesion an attempt was made to record the action potential from the nerve above the wrist when the digital nerves of the fifth finger were stimulated by a ring electrode. No response to stimulation was found in this group. This was also true in 8 patients in whom the nerve was stimulated at the wrist, including the 1 patient with normal motor conduction time.

The authors' experience with the clinical application of this technique has been encouraging. In patients with an ulnar nerve lesion and definite atrophy, a slowing of motor conduction has usually been demonstrated, and in those with no wasting, direct recording of nerve action potentials has shown evidence of a lesion. However, the degree of damage must be sufficient to produce loss either of power or of sensation. In those patients who have only pain and paresthesias, the level of the lesion cannot be localized.

—*Robert G. Ojemann, M.D.*

SYMPATHETIC NERVES

Future Place of Lumbar Sympathectomy in Obliterative Vascular Disease of Lower Limbs. J. A. GILLESPIE. *Brit. M. J.*, 1960, 2: 1640.

ONE HUNDRED consecutive cases of obliterative vascular disease of the lower extremities treated by sympathectomy are reviewed 1 to 7 years after operation. Results are assessed in terms of the indication for surgery, i.e., claudication or skin lesions. The low rate, 13 per cent, of improvement of claudication was regarded as possibly fortuitous and not necessarily related to sympathectomy. Fifty-five per cent of skin lesions healed after sympathectomy in this series, but the author emphasizes the importance of selection of cases in this group.

Vascular disease of the lower limbs often coexists with vascular disease elsewhere, particularly in the coronary and cerebral vessels, which is commonly the cause of death in these patients. The average age at death of 25 patients was 57 years.

—*Raymond N. Kjellberg, M.D.*

SURGERY OF THE INTEGUMENT AND CONNECTIVE TISSUES

SKIN AND SOFT TISSUES

Five Years of Prophylaxis: Why Are There Still Decubitus Ulcers? (Cinq années de prophylaxie: pourquoi y a-t-il encore des escarres de décubitus). R. VILAIN. *Sem. hôp. Paris*, 1960, 36: 3296.

THE AUTHOR is amazed that decubitus ulcers still occur despite the numerous articles, conferences, and crusades on this subject. He agrees with other authors that the pathogenesis is the prolonged compression of soft tissues, which leads to venous blockage followed by congestion, edema, inflammation, and finally necrosis.

He presents several reasons for the failure of prevention of decubitus ulcers. Foremost is the complete disinterest of some members of the medical profession. No attempt is made at prevention in the susceptible case. Areas of the body that are exposed to pressure should be observed daily. The first indication of a pressure sore is often misinterpreted or neglected. This sign usually consists of an erythematous spot with or without superficial loss of epithelium. If this stage is recognized and the area is treated early, ulceration can be prevented. The author recommends the local use of chymotrypsin by hypodermic injection. He condemns the use of antiseptics and rubber rings. The latter further impede the circulation at the periphery of the lesion. He recommends very strongly the use of massage and intermittent pressure mattresses in prevention and treatment. The mattresses should be checked frequently for proper functioning. Frequent change of position is more important than the ideal position, despite the protests of the patient and his entourage. These changes should include the frequent use of the ventral position.

—Joseph J. Bahuth, M.D.

A Clinical and Histological Investigation into the Fate of Epithelial Elements Buried Following the Grafting of "Shaved" Skin Surfaces. NOEL THOMPSON. *Brit. J. Plast. Surg.*, 1960, 13: 219.

IN 1956 Hynes introduced a method of "shaving" and skin grafting whereby a cutaneous mole or scar from which the surface epithelium and immediately subjacent dermis or scar tissue has been removed is treated by the application of a split-skin graft from another site. In this clinical study, this method has been used to assist the healing of thick split-skin graft donor sites.

This technique involves the burying of epidermal appendages—hair follicles and sebaceous and sweat glands—under the surface graft. In order to determine the fate of such buried epithelial elements, serial biopsies of grafted donor sites were subjected to histologic examination. In addition, a series of patients having scars or nevi treated by shaving and skin grafting were followed up to assess the incidence of postoperative clinical complications.

The author concludes that the rate and quality of healing of split-skin graft donor sites is improved by the application of Thiersch grafts. The burying of epithelial elements in the operation of "shaving" and skin grafting is followed routinely by the formation of microscopic epidermoid cysts, but these undergo spontaneous dissolution within a year in the vast majority of cases. In only 34 per cent of patients did clinically persistent epidermoid cysts require operative removal.

After the application of Thiersch grafts to areas of partial thickness skin loss, some host sweat glands regenerate to discharge their secretion to the surface, but most do not; the latter, though continuing to survive and function, probably have their secretion internally resorbed into the local circulation. Under the same circumstances only a minimum number of hair follicles survive as functional units.

—Carl Schiller, M.D.

Flagellation and Free Grafting. THOMAS GIBSON. *Brit. J. Plast. Surg.*, 1960, 13: 195.

THE USE of flagellation, or preoperative beating as a means of "increasing the vitality" of a massive graft is not only of great historic interest but also a possible pointer to the solution of this still intractable problem of massive free grafts.

In analyzing the physiologic basis for reported results, the author comments that preoperative beating will cause a paralysis of the muscular coat and prevent spasm of vessel walls. Also, the vessel mouths on the cut surface will be patent and ready to form early anastomoses with vessels in the bed. Second, the vascular network in the beaten graft is full of blood. Last, marked edema accompanies the congestion after the beating. Until a circulation is developed, the cells of a graft depend for their nourishment on the intercellular fluid, and the great increase in this may be of value in tiding the cells over the initial period of starvation.

The author has tried this method in a small series of cases in an effort to enhance the take of free fat grafts, which has always been notoriously poor. The series is small and so far shows that some grafts have undergone absorption but that many have survived unchanged. No conclusions can yet be drawn.

This account of a little known chapter in medical history is given so that it may stimulate further research into one of our major unsolved problems, the survival of the massive free graft.

—Carl Schiller, M.D.

Is Graft Donor's Blood an Enhancing Agent for Homologous Grafts? CLARENCE W. MONROE, RICHARD H. ANDRESEN, GEORGE M. HASS, DOROTHY A. MADDEN, and SOPHIA PAPADOPOULOS. *Plast. & Reconstr. Surg.*, 1960, 26: 388.

THE AUTHORS PRESENT a simple, straightforward report of research utilizing rabbits. Skin was grafted from one rabbit to another by homografts. The recipient rabbits had received blood from the donor rabbits. This was done because previous investigations in humans and in animals had shown that skin grafts

lived longer as homografts when the donor's blood had been transfused to the recipient. Medawar has stated that there may be an increased tolerance in the donor under these conditions due to the paralysis of the immune mechanism.

The authors had previously reported the use of musculofascial grafts in the same manner in another report. They noted that musculofascial and skin homografts are comparable in the response they elicit in the rabbit if one makes due allowance for the presence of infection in an open wound and the very complicated nature of skin as contrasted to musculofascia. Their experience was that the exchange of blood between 2 animals before crossgrafting them produces a consistent pattern in homologous response and that it is different from that in the untransfused animal. Though the graft may be copiously vascularized by the host, there is no deposition of fibroblasts or collagen and, therefore, minimal organization of the graft by the host tissues. This appears to the authors as the most complete rejection of homologous tissues that they have been able to produce to date in the laboratory.

The transplanted skin in those animals that had been transfused was accepted for a longer period but not indefinitely. This is a thought provoking and logical approach to an extremely important problem for the protection of man in peace and war.

—Henry S. Patton, M.D.

Melanoblastomas, Their Meaning and Treatment (Melanoblastome, ihre Redeutung und Behandlung). ERICH SODER and GERHARD OTT. *Langenbecks Arch. klin. Chir.*, 1960, 294: 582.

THE AUTHORS REPORT on 130 patients with melanoma seen at the Heidelberg University Clinic, Heidelberg, Germany. The average age of the patients was 42; those with carcinoma were younger. There was no sex predilection. The melanomas occurred mainly on the feet, legs, face, choroid of the eye, and vulva. Over half of the patients had noticed a freckle or birthmark for years prior to the melanoma; the authors believe that most melanomas develop from benign nevi.

At least 90 per cent of adults have some nevi; it is not known which ones become malignant and why. The clinician should be suspicious of all of them, but particularly one that becomes bigger or blacker or which bleeds easily, or if regional lymph nodes enlarge. Trauma of one sort or another is implicated in malignant change in some cases. The authors found cases in which small benign growths, present for years, changed after bruising, incision biopsies, or cauterizations. A hen picked at a small brown spot on one man's leg; the lesion suddenly started to grow, and inguinal lymphadenopathy with metastatic melanoma developed.

Melanomas spread rapidly to lymph nodes and skin, less often through the blood to lungs, bones, and brain. These tumors are radioresistant. Treatment should consist of wide excision in three planes. Local infiltration for anesthesia is not good because the surgeon may disseminate tumor cells with the needle; likewise he must not disturb the tumor with his other instruments. The excision should be made without regard to the subsequent closure. It should be followed "early"—which time the authors do not specify—by en bloc regional lymph node dissection.

The authors tried hypophysial ablation by electrocoagulation or radioactive gold in 20 patients with advanced disease with little evidence of benefit.

The authors had a 5 year survival rate of 40 per cent, although 28 per cent of the patients had demonstrable metastasis on their first clinical visit. The 5 year survival is no guarantee of cure, however; 9 5 year survivors died later of their disease.

—William B. Gallagher, M.D.

PLASTIC REPAIR

One Stage Pollicisation of Little Finger. I. KAPLAN and J. PLASCHKES. *Brit. J. Plast. Surg.*, 1960, 13: 272.

THE AUTHORS have developed an experimental, 1 stage pollicization of digits performed in a small series of monkeys. Their technique follows very closely the neurovascular bundle technique of Littler. In one instance they transferred the fifth digit to the thumb in a human being with success but with a very short follow-up period. The photograph of this result shows the finger when it is still swollen on the tenth postoperative day. *—Henry S. Patton, M.D.*

BREAST

Intermittent Precocious Breast Development Associated with Mild Bronchitis. FRANCESCA BRAMBILLA, JEANNE A. EPSTEIN, and HERBERT S. KUPPERMAN. *J. Clin. Endocr.*, 1961, 21: 80.

PRECOCIOUS BREAST DEVELOPMENT may result from systemic disease involving the liver, brain, or lungs. The case is presented of a 4 year old girl who had periodic episodes of breast enlargement during attacks of mild respiratory infection. Hypersecretion of gonadotropin and estrogen was associated with the attacks.

Gynecomastia has been reported in association with pulmonary neoplasm, tuberculous infection of the lung, pulmonary abscess, and other more rare conditions.

The pulmonary stimulus remains unknown, but it has been suggested that it is endocrine in nature, a toxic, allergic, or stress reaction or perhaps a neurogenic stimulus. The nature of the pituitary hormone released by this unknown stimulus is also in question. There is not adequate evidence to suggest that it is luteinizing hormone, prolactin, or follicle stimulating hormone (FSH). A discussion of these various theories is included in the report. *—John H. Davis, M.D.*

Experience with Mammography in a Tumor Institution. ROBERT L. EGAN. *Radiology*, 1960, 75: 894.

IN AN ATTEMPT to estimate the reliability of mammography as a diagnostic tool, 1,000 consecutive roentgenographic examinations of the breast were analyzed. These had been performed at the University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas between May 1956 and May 1959. Adequate follow-up was available on all except 2 patients who were excluded from the series since both were examined in the terminal state of malignant lymphoma and without either biopsy or autopsy.

The technique of examination is described, the significant features of which are high detail film, close coning of the roentgen ray beam, low kilovoltage of 22 to 34, and omission of added filtration.

There were 245 proved carcinomas, all but 7 of which were correctly diagnosed by mammography. Of the 7 errors, 5 were in patients whose tumor had been removed at the time of biopsy, prior to the mammography, and no residual carcinoma was found in the postirradiated radical mastectomy specimen. Malignant tumors were found in 19 breasts clinically considered to be negative.

There were 430 benign lesions and 20 errors in diagnosis in this group. False positives, benign lesions called malignant, were the greatest source of error. These lesions included abscesses, infected cysts, or fibrocystic disease associated with marked sclerosing adenosis or ductal hyperplasia.

Of 4 cases of Paget's disease of the nipple the underlying carcinoma was not detected clinically in 3 but was diagnosed by roentgenographic examination in all 4. The smallest carcinoma demonstrated by roentgen rays was 8 mm. in diameter on sectioning. The presence of stippled calcification led to the diagnosis.

The demonstration of axillary nodes by roentgenography is not, in itself, a diagnostic criterion of malignant lesions. In 108 cases axillary nodes were demonstrated by roentgen rays and found to be carcinomatous upon histopathologic study in 88.

Experience has shown mammography to be a simple method of demonstration of a breast lesion with a high accuracy in prediction of its type. In this series of 1,000, the error in malignant disease was less than 1 per cent, and 19 clinically unsuspected carcinomas were found. —*Lois Cowan Collins, M.D.*

Ovarian Cortical Hyperplasia and Cancer of the Breast (Hyperplasie du stroma cortical de l'ovaire et cancer du sein). M. SOMERHAUSEN and C. GOMPEL. *Bull. Soc. Roy. belg. gyn. obst.*, 1960, 30: 467.

TWENTY-ONE WOMEN afflicted with cancer of the breast in the process of generalization were treated on the authors' service by bilateral ovariectomy and adrenalectomy. The ovarian tissues were examined for cortical hyperplasia.

When the results of these examinations were tabulated it was found that ovarian cortical hyperplasia was present in 86 per cent of the women with cancer of the breast and in 50 per cent of the controls.

The authors conclude that the intimate relationship between the cortical stroma of the ovary and cancer in the female, as first reported by G. V. S. Smith, must, despite the fact that they report only 21 instances, be accepted with reserve.

—*John W. Brennan, M.D.*

Treatment of Carcinoma of the Breast with Radiation with or Without Limited Excision of the Tumor (Le traitement du cancer du sein par les rayons X employés seuls). H. DANCOT, J. HENRY, and L. LAUWERS. *Acta chir. belg.*, 1960, 59: 481.

THIS REPORT from the Institute Bordet in Brussels, Belgium concerns 89 patients with carcinoma of the breast who between 1947 and 1956 were treated with radiation as the primary mode of therapy. The technique consisted of tangential irradiation of the breast and irradiation of the internal mammary chain, the apex of the axilla, and the subclavicular region. In some cases excisional biopsy of the cancer preceded therapy.

At the end of 5 years 39 per cent of 58 patients were apparently cured. In stage I the 5 year cure rate was 73 per cent and in stage II, 37 per cent. Local tumor recurrence in treated lesions, otherwise classified as operable, was 13 per cent and for nonoperable tumors the recurrence rate rose to 24 per cent. All recurrences appeared within 3 years and usually during the first. Of 11 patients with inframammary carcinomas, 5 were alive and well at 3 to 5 years.

Complications among the 89 patients consisted of brachial neuritis in 5 instances, painful radiation contracture in 8, cutaneous necrosis in 2, and edema of the arm in 1.

The authors consider these results to compare favorably with those obtained by surgical means. They stress the absence of delayed local recurrence and the effectiveness of this form of therapy in controlling inframammary cancer and involvement of the nodes of the axillary and mediastinal regions.

—*John H. Wulsin, M.D.*

SURGERY OF THE THORAX

TRACHEA, LUNGS, AND PLEURA

Permanent Tracheostomy in the Treatment of Pulmonary Insufficiency. ARTHUR Q. PENTAY and EDGAR MAYER. *Ann. Otol. Rhinol.*, 1960, 69: 1157.

AN ELECTIVE OPERATION in which an opening is created in the trachea by means of a mucocutaneous plastic procedure which results in a firm stoma that can be permanent if necessary is recommended for use in treating patients with progressive pulmonary insufficiency. The operative technique includes the fashioning of the upper flap so that it is redundant enough to allow infolding into the tracheal opening when the head is slightly flexed, the removal of a window-like section of the trachea 2 cm. in diameter, if possible, resection of the anterior and lateral wall of the trachea at the second and third tracheal cartilages to create the 2 to 2.5 cm. opening, and the proper cuffing and suturing of the skin margins to the mucosal surface of the trachea. The partial occlusion of the tracheal opening will allow the patient to carry on normal conversation; when aspiration of the catheter is desirable the patient extends the head and the flap moves upward out of the tracheal stoma.

Permanent tracheostomy with suctioning for chronic advanced lung insufficiency is chiefly a palliative measure for the patient with advanced pulmonary disease, but on a few occasions it has proved successful in rehabilitating patients.

—*W. Foster Montgomery, M.D.*

Microlithiasis in Pulmonary Alveoli Demonstrated by Biopsy (Micro-lithiase alvéolaire pulmonaire démontrée par biopsie). R. ISRAEL-ASSELAIN, J. CHEBAT, R. ABELANET, and J. LECHIEN. *J. fr. méd. chir. thorac.*, 1960, 14: 635.

THERE ARE 80 cases of microlithiasis of the pulmonary alveoli reported in the literature and, of these, 69 have been carefully studied. The authors report 1 case and review the literature. The lesion occurs in all age groups, but most cases have been described in children between 6 and 9 years of age. No cases have been reported in patients less than 6 years old. The sex incidence favors females in the ratio of 4 to 3. There is a familial tendency to the disease. One report in the literature concerns 10 cases from 2 families.

The lesion is generally asymptomatic. It is usually discovered on roentgenographic examination. Occasionally in older people hemoptysis may occur and occasionally there is a cough productive of sputum. In only 1 case in the literature were the microliths recovered in the sputum. In advanced cases there is respiratory insufficiency manifested by right heart failure. Two of the patients in the literature died at an early age of pulmonary insufficiency. Paradoxically, pulmonary infections are rare, and usually bacteriologic studies of sputum are unrevealing.

Roentgenologic examination shows finely disseminated calculi throughout the lungs with prominent trabeculations radiating from the hilus on each side. There is usually absence of lymphadenopathy on tomography. The lesion must be differentiated from tuberculosis, cancer, sarcoid, pneumoconiosis, hemosiderosis, and histoplasmosis. Parathyroid disease is not associated with microlithiasis, nor is there any correlation between this condition and visceral or arterial calcification or changes in the calcium deposits in bone. Occasionally the condition is associated with renal calculi. Bronchoscopic studies are uniformly negative in this disease. Pulmonary function studies show decrease in the total capacity and the vital capacity, augmentation of the residual volume, normal maximum ventilation, and diminished capacity of diffusion of gases.

The pathogenesis of this lesion is complex. A protein matrix forms and on this there is calcium deposition. The excretion of carbon dioxide by the lungs probably produces a local acidosis favoring this calcium precipitation.

Treatment of this condition is without effect. Corticoids have been tried without success. Fortunately, the condition usually does not require treatment.

—*Frederick W. Preston, M.D.*

Electrocardiographic Changes in Bronchial Carcinoma (EKG-Veraenderungen beim Bronchialcarcinom). W. KAULBACH and E. NIEGTSCH. *Langenbecks Arch. klin. Chir.*, 1960, 296: 102.

STIMULATED by the fact that very little has been published about the changes in the EKG-pattern in patients with bronchial cancer, a team from the Surgical University Hospital of Heidelberg, Germany reports its findings in 323 patients.

The electrocardiograms of 202 patients, or 62.5 per cent, revealed pathologic changes. Of these patients, 53.5 per cent were operated upon but only one-third of them were considered operable. The average age was found to be 56.6 years.

The remaining 121 patients, or 37.5 per cent, had a normal EKG-pattern. Three-fourths of these underwent operation and 43 per cent were considered operable. The average age was calculated to be 54.9 years.

In the group with pathologic EKG tracings 106 patients showed signs of myocardial damage. Seventy-one patients out of both groups had a tachycardia and 66 per cent of these turned out to be inoperable, thus pointing out the poorer prognosis in patients with this disorder. Thirty-three patients had changes caused by systemic hypertension and pulmonary emphysema. Low voltage was present in 27.

In order of frequency the following additional changes were found: P—pulmonale, heart block, frequent extrasystoles, left bundle branch block, and bradycardia.

The most frequent postoperative complications are mentioned and briefly discussed. One typical case with illustrations of the electrocardiograms and roentgenograms is included.

The authors believe that the electrocardiogram is a

valuable diagnostic tool although in none of the cases was it a contraindication for thoracotomy.

—Hans J. Schweizer, M.D.

Endobronchial Malignant Lymphoma. MELVIN L. SAMUELS, CLIFTON D. HOWE, GERALD D. DODD, JR., LILLIAN M. FULLER, and Others. *Am. J. Roentg.*, 1961, 85: 87.

FOUR CASES of malignant lymphoma in which the patient had massive endobronchial lesions and 1 in which the patient had bronchostenosis are described. The disease was characterized by persistent, dry, irritating cough, usually associated with dyspnea and with the physical and roentgenographic findings of atelectasis. The roentgenographic findings did not differ from those of atelectasis due to other causes. It has not been widely emphasized that endobronchial disease is usually responsible for the atelectasis and that pressure from enlarged mediastinal lymph nodes does not play a significant part in the bronchial occlusion.

Bronchoscopy revealed obstructive lesions in 4 cases and extramucosal constriction in the remaining case. Biopsy was definitive in only 1 case.

Criteria for adequate therapy are postulated. It is urged that treatment be given initially to uncomplicated mediastinal lymphadenopathy. Failure may result in recurrence with complicating endobronchial involvement.

Endobronchial involvement dominated the initial pulmonary manifestations in 3 instances and probably indicated extremely virulent disease. Therapy in palliative doses is usually adequate to control pulmonary manifestations in such cases.

—W. Foster Montgomery, M.D.

HEART AND PERICARDIUM

Congenital Tricuspid Stenosis. RODNEY A. GOMEZ and ALFREDO LEPORE. *J. Philippine M. Ass.*, 1960, 36: 843.

THE AUTHORS describe the clinical and pathologic findings in 9 cases of congenital tricuspid stenosis from among a total of 2,000 admissions for cardiac reasons to St. Francis Hospital, Reslyn, New York, over a 4 year period.

Dyspnea either accompanies or ushers the neurologic and cardiopulmonary symptoms, and precipitates or aggravates the cyanosis. Cardiac murmurs may or may not be present since they depend upon the intrinsic anatomic defects, the amount of flow, and the pressures on each side of the defects. Peaked P waves and left ventricular hypertrophy with left axis deviation are the most constant electrocardiographic manifestations. The nonspecific cardiac enlargement observed on chest roentgenograms is usually composed of right atrial prominence and left ventricular enlargement. Distinct and prolonged opacification of an enlarged vena cava and a dilated hepatic vein, and initial dimpling of the dye at the right atrioventricular boundary are the more common angiocardiographic findings. Early opacification of the left side of the heart and the left aorta is indicative of a right-to-left shunt which is usually at the atrial level. The right ventricle is always entered with difficulty during cardiac catheterization. A right atrioventricular gradient is always found, since the end-diastolic right ventricular pressure is most often higher than the mean right atrial pressure. Stenosis of the valvular tissue was always present in some degree, the tricuspid leaflets usually being small, fused, and thickened. The average orificial diameter was 1.1 cm.

The various surgical procedures attempt to correct the physiologic difficulties by increasing the pulmonary flow to combat the gross desaturation. Patients with associated congenital systemic-pulmonary shunts are not usually benefited by a Blalock or Potts-Gibson procedure. Some reports indicate that in the absence of this type of shunt, anastomosis of the superior vena cava to the distal end of the right pulmonary artery may be beneficial.

—Stephen W. Carveth, M.D.

Review of 1,000 Operations for Mitral Stenosis (Ueberblick ueber 1000 operierte Mitralstenosen). W. IRMER, R. M. KONRAD, and F. ROTTHOFF. *Langenbecks Arch. klin. Chir.*, 1960, 296: 154.

THIS IS an extensive review of 1,000 patients operated upon for mitral stenosis at the Surgical Clinic of Düsseldorf, Germany during the 8 year period from 1951 to 1959.

The technique used was that of left-sided anterolateral or posterolateral thoracotomy and digital fracture of the mitral valve through the left auricular appendage. In 51.9 per cent of the cases guillotine knives were used. Only occasionally was the approach from the right through the interatrial groove used.

Quantitative estimation of concomitant mitral insufficiency and the combination of mitral stenosis with other valvular lesions are discussed thoroughly. Indications and contraindications and the specific problems in pregnancy are reviewed. Seventy per cent of the patients had class III lesions and 20 per cent class IV lesions according to the classification of the American Heart Association.

Of the valves 42.7 per cent showed good mobility, 14 per cent were affected by funnel-shaped stenoses, and 7 per cent did not allow dilatation because of thrombi, narrow appendage, scarring, or predominant insufficiency.

The relative merits of intraoperative pressure measurement in the left atrium and the many intraoperative and postoperative complications are described. The over-all mortality was found to be 6.5 per cent; without class IV cases it was 2.6 per cent. A large section is devoted to the different causes of death.

Follow-up results and an extensive bibliography conclude this fine article.—*Hans J. Schweizer, M.D.*

Elective Hypothermic Cardiac Arrest in Normothermic Animals. WILLIAM F. BERNHARD, HANS F. SCHWARZ, and NETAR P. MALLICK. *Ann. Surg.*, 1961, 153: 43.

THIS ARTICLE describes a group of experiments which provide a method for the production of hypothermic cardiac arrest using intermittent coronary perfusion with cold oxygenated blood. The article also includes an evaluation of myocardial oxygen utilization in the normothermic, rhythmically contracting heart and during cold induced cardiac arrest.

The elective arrest of cardiac muscular activity during cardiopulmonary bypass is an important adjunct for the surgical correction of certain intracardiac lesions. Current methods in use consist of an intracoronary infusion of potassium citrate or anoxic arrest produced by cross-clamping the aorta distal to the sinuses of Valsalva.

Selective hypothermic arrest produced by coronary perfusion with cold oxygenated blood is described as an effective safe alternative. A dry quiet operative field can be obtained utilizing intermittent perfusion over periods of 50 to 90 minutes with multiple interruptions of flow for intervals of 10 to 25 minutes. After cardiac rewarming, conversion from ventricular fibrillation to a sinus rhythm is accomplished easily. Decompression of the left side of the heart proved to be essential in this study to prevent pulmonary congestion from bronchial collateral flow.

A second part of this study evaluated myocardial metabolic requirements. The oxygen utilization of the heart performing external work at normal temperature is reported to be 9.0 c.c./100 gm. of myocardium/min. When relieved of external work, the oxygen utilization decreases to 3.4 c.c. or 38 per cent of the original requirement. A further reduction occurs during cardiac arrest at normal temperature. This is produced with a potassium chloride perfusate and yields an oxygen consumption of 2.2. c.c. or 24 per cent of the normal consumption. The authors found that during cardiopulmonary bypass the normothermic, empty, rhythmically contracting heart extracts 3.9 c.c. of oxygen/100 gm. of whole heart/min. After the induction of hypothermic arrest, at a mean temperature of 12 degrees C. the myocardial oxygen consumption is reduced to 1.6 c.c. This value represents 18 per cent of the oxygen consumption of the working heart at normal temperatures. A comparison of the data obtained in the hypothermic and normothermic arrested hearts indicates that a reduction in temperature per se is associated with a relatively small diminution in oxygen utilization. The authors conclude that the method which provides oxygen and substrates for the myocardium would seem to be a physiologically sound solution to the problem of prolonged cardioplegia. —*Donald M. Clough, M.D.*

The Surgical Repair of Ruptured Aortic Sinus Aneurysms Using Total Cardiopulmonary Bypass. JEROME HAROLD KAY and OSCAR MAGIDSON. *West. J. Surg.*, 1960, 68: 365.

AORTIC SINUS ANEURYSMS are usually congenital and most commonly arise from the right coronary sinus. The next most frequent site of origin is the noncoronary sinus and rarely the condition arises in the left coronary sinus. The aneurysms are usually small and protrude finger-like into the right ventricle or atrium.

The diagnosis can usually be made by simple clinical means, chiefly, by exclusion of other lesions causing continuous murmur. It may be substantiated by demonstrating the arterial venous shunt into the right atrium or right ventricle by means of catheterization of the right side of the heart and by delineating the pathway of the shunt by means of a retrograde aortogram.

The prognosis after rupture is variable. The patients may live for days to many years. The average age at autopsy is about 35 years. Details of the history, physical examination, and surgical technique utilizing cardiopulmonary bypass are reported in 4 cases of ruptured sinus of Valsalva aneurysm. All patients are now cured and living normal lives.

—*Wayne F. Cameron, M.D.*

Nontraumatic Hemopericardium. BENJAMIN H. BARBOUR, ALBERT E. HIRST, JR., and VARNER J. JOHNS, JR. *Am. J. Cardiol.*, 1961, 7: 102.

ONE HUNDRED FIVE CASES of nontraumatic hemopericardium were encountered among 21,000 consecutive autopsies at the Los Angeles County Hospital, Los Angeles, California. The causes in order of frequency were acute myocardial infarction in 63, and ruptured aneurysm in 35, of which 30 were of the dissecting type. There were 4 syphilitic aneurysms and 1 mycotic aneurysm of a coronary artery. Hemopericardium was the result of metastatic carcinoma in 4 and of a blood dyscrasia in 3 cases.

In most cases hemopericardium was sudden in onset and massive in amount, giving rise to a rapidly fatal cardiac tamponade. Thus, in only 4 cases was a correct clinical diagnosis made, based on the recognition of the typical symptoms and signs of pericardial effusion.

As in other series, the patients with myocardial infarction terminating in cardiac rupture were elderly; no patient was below the age of 50 years. A slight preponderance in women was noted.

—*Harold Laufman, M.D.*

Chronic Constrictive Pericarditis. PAUL WOOD. *Am. J. Cardiol.*, 1961, 7: 48.

A SERIES of 40 cases of constrictive pericarditis is analyzed. One-quarter of the cases were still in the active stage of disease. A paradoxical pulse, a dominant and sharp x descent in the jugular pulse, normal rhythm, more than slight enlargement of the heart shadow, and persistent hydrothorax were noted more commonly in the group with active pericarditis. Atrial fibrillation, a relatively small heart and pericardial calcification strongly indicated inactive cases of long duration. An early third heart sound and a characteristic electrocardiographic pattern occurred with equal frequency in both groups.

In differential diagnosis, perhaps the only serious difficulty is in distinguishing constrictive pericarditis from cardiomyopathy of clinically obscure origin. Factors indicating cardiomyopathy are a conspicuous left ventricular cardiac impulse, a third heart sound falling at its usual time, mitral or tricuspid regurgitation, bundle branch block, electrocardiographic changes denoting left ventricular hypertrophy or necrosis, and more than slight cardiac enlargement roentgenologically.

In the absence of thromboembolic pulmonary hypertension, the left atrial pressure is usually 10 to 20 mm. Hg higher than the right in cases of cardiomyopathy, the divergence increasing with exercise; in chronic constrictive pericarditis the two atrial pressures usually remain similar under all conditions. The implication that cardiomyopathic heart failure

is initially and predominantly left-sided is accepted. The cardiac output averages about 25 per cent lower and the arteriovenous oxygen difference 33 per cent higher in cardiomyopathy than in chronic constrictive pericarditis. The maintenance of a resting cardiac output well over 4 L./minute when there is atrial fibrillation is characteristic of constrictive pericarditis.

The mortality from pericardiectomy was 11 per cent in the 27 patients treated surgically. The results were good or excellent in 82 per cent and poor or indifferent in 7 per cent. Reconstriction was not observed. Activity is no bar to successful surgical therapy; none of the 7 patients with active pericarditis operated upon in this series died.

—*Harold Laufman, M.D.*

Chronic Constrictive Pericarditis. Ilmo Louhimo, Pentti Koskelo, and Erkki Laustela. *Ann. chir. gyn. fenn.*, 1960, 49: 416.

The authors report observations on 33 patients with chronic constrictive pericarditis treated during a period from 1945 to 1957. Twenty-six of these patients were operated upon. The authors discuss the history of the disease briefly and present data on the symptoms and signs which lead to the diagnosis of chronic constrictive pericarditis. They also studied the vicissitudes of patients after treatment.

Of these 33 patients 64 per cent were male. Thirteen patients had a history of tuberculosis although the specimen taken at operation confirmed this cause in only 4 cases. Chest injury was the most probable cause in 2 cases, and extensive roentgenotherapy accounted for 1. A history of previous rheumatic fever was present in 2 cases but there were no auscultatory signs of valvular heart disease in these patients. In 15 cases there were no hints as to possible cause. In 10 of the cases a history of acute pericarditis preceded the chronic phase.

The most common symptoms complained of by the patients were dyspnea on exertion, edema of legs, and abdominal swelling. The general condition of 10 patients was poor at the time of the first physical examination. Peripheral cyanosis was seen in 13 patients and a constant clinical feature was venous stasis. An elevated venous pressure and/or distention of neck veins in the upright position were seen in every case. The liver was enlarged in 32 cases. The blood pressure was usually low. In 24 cases pleural effusion was shown by roentgenography, and in 22 cases the heart was enlarged. The authors also discuss the electrocardiographic findings.

Operation was carried out on 26 of 33 patients and in all except 1 an extrapleural pericardectomy was performed. The extent of decortication was usually limited to the anterior aspect of the heart. Six patients died in connection with the operation, the operative mortality thus being 23 per cent. Forty-six per cent of the operated upon patients were dead within 3 years. Of the nonoperated upon group of 7 patients 1 patient was still alive 11 years later, and 1 other survived 4 years.

Follow-up examinations were performed on 13 of 14 surviving patients. In 5 patients the result of the operation was good and in 2 of them it was excellent. In 4 cases there was a moderate result, but the patients derived considerable benefit from the operation. The result was poor in 4 cases.

—*Donald M. Clough, M.D.*

Chronic Constrictive Pericarditis Treated with Pericardiectomy. Donald B. Effler. *Am. J. Cardiol.*, 1961, 7: 62.

During the past 10 years 26 patients were operated upon at the Cleveland Clinic Hospital, Cleveland, Ohio for the surgical correction of chronic constrictive pericarditis. There was considerable variation in technical features of the operation, but with increasing experience the trend was toward one of two basic incisions: (1) the median sternotomy—sternal-splitting—or (2) the transverse sternotomy—sternal transection. Either incision provided excellent exposure.

Successful decortication is dependent upon the surgical exposure; however, other factors may be of equal significance. The most important of these is the character of the pericardial disease in the patient. The ability to establish a cleavage plane is usually dependent upon the pathologic process itself. Other reasons for failure are myocardial disease and postoperative complications.

The cause of chronic constrictive pericarditis is still a matter of interest. Although tuberculous pericarditis was originally presumed to be the responsible cause of constrictive pericarditis, it now appears that this may be comparatively rare. Comparison of a sizable series of patients with acute pericardial effusion treated during the same time interval suggests a possible relationship between acute hemorrhagic pericarditis and chronic constrictive pericarditis. The investigative problem remains to establish the common cause of acute pericardial hemorrhage and the factors that allow intrapericardial blood to incite a possible constrictive pericarditis.

—*Harold Laufman, M.D.*

ESOPHAGUS AND MEDIASTINUM

Treatment of Esophageal Strictures. Daniel C. Baker, Jr., and George C. Hennig. *Ann. Otol. Rhinol.*, 1960, 69: 1127.

The technique used and described by Crump and Hennig employs instruments devised by Crump which include a flexible tip wire, a flexible hollow carrier for the wire, a knob-tipped staff wire with a central opening through the knob, and a hollow staff carrier to which metal bougies with a central opening can be attached. Retrograde curettes have also been devised with which the same staff carrier may be used.

The hollow, flexible metal carrier is passed to the site of the obstruction after being introduced into the esophagus with the patient in a sitting position and the head hyperextended. The flexible tipped wire may then be introduced through the lumen of the carrier until it reaches a point of resistance. The carrier is then withdrawn a few centimeters and the flexible tipped wire gently rotated until it finds the lumen, then it is advanced past the obstruction. The carrier can then be advanced past the obstruction and this operation repeated until the wire reaches the stomach. The introduced wire makes a firm guide for

metal bougies or olives and provides for safe and effective dilatation. —*W. Foster Montgomery, M.D.*

Primary Intrathoracic Neural Tumors. B. T. Le Roux. *Thorax*, Lond., 1960, 15: 339.

Excluding retrosternal goiter, primary intrathoracic neural tumors are the commonest mediastinal abnormality, comprising 30 to 35 per cent of mediastinal cysts and tumors. Benign neural tumors constitute more than 75 per cent of abnormalities in the posterior mediastinum. Benign nerve cell tumors are found most commonly in the second and third decades, whereas nerve sheath tumors occur most frequently during the third, fourth, and fifth decades of life. About 10 per cent of intrathoracic neural tumors are malignant and these most commonly occur in the first 4 years of life. More than 60 per cent of all neural tumors in the chest are of nerve sheath origin, either neurilemmomas or neurofibromas. These tumors are most common in females; the ratio is almost 2 to 1.

Although these lesions are most commonly incidental findings and asymptomatic, when symptoms are present they are most frequently referable to the respiratory system. Neurologic symptoms are usually rare in this disease. However, 1 patient in this series with a benign neurilemmoma had Pancoast's syndrome. There has been one report in the literature of a patient with a neural tumor and hypertrophic pulmonary osteoarthropathy.

Thirty patients are presented in this review, all of whom underwent surgical extirpation of the lesion. Twenty-nine are living and well. Weakness of the legs was found postoperatively in 1 patient, but lasted for only a few days. In this patient, three intercostal vessels had been divided. —*Frank J. Milloy, M.D.*

Intrathoracic Neurogenic Tumors (I tumori neurogenici intratoracici). Piero De Albertis and Ennio Gandolfo. *Minerva med.*, Tor., 1960, 51: 3537.

The neurogenic tumors of the mediastinum account for approximately 30 per cent of all mediastinal masses seen on standard roentgenograms. In most instances their discovery is an accidental finding on routine roentgenography, since these tumors in the early stages are almost invariably asymptomatic. The differential diagnosis from other pathologic conditions of the mediastinum is a challenging problem to the roentgenologist and represents the subject of this article.

The diagnostic criteria and the techniques used at the department of radiology of the University of Genoa Medical School, Genoa, Italy are here reported. Because of the retrohilar position of this type of tumor, tomography is of paramount importance for a correct diagnosis. Tridimensional tomography, lateral, frontal, and axial, has been employed routinely by the authors in the investigation of these tumors and diagnostic pneumothorax has been used on occasions. With these techniques the tumors appear as a well-defined, round or oval mass located in the posterior mediastinum, most commonly in the middle lung field on the left side. There is one type of neurogenic tumor which does not follow the rule: the neurinoma of the intercostal nerves, typically located anteriorly. The roentgenographic appearance of this tumor is that of a well-defined round mass located at the periphery of the lung field.

Once again the combination of pneumothorax and stratigraphy proved to be most useful in the hands of the author. A few roentgenograms illustrating the types of tumor are presented.

—*Riccardo Benvenuto, M.D.*

SURGERY OF THE ABDOMEN

ABDOMINAL WALL, PERITONEUM, AND HERNIA

Dermatome Flap in the Treatment of Large Incisional Hernias (Der Dermatomlappen bei der Behandlung von grossen Narbenbruechen). MARTIN ZWICKER. *Münch. med. Wschr.*, 1960, 102: 2552.

DESPITE antibiotics and improved operative techniques, incisional hernias are not always avoidable. The usual repair by means of mobilization and flap formation is not always applicable; this occurs in less than 5 per cent of the cases. Various transplants, using silver, tantalum, and synthetic material have been used. Use of autoplastic transplants of fascia has been abandoned because they respond to tension in only one direction.

Rehn and his associates have developed a cutis plastic simplified by use of a dermatome. The original technique consisted of dividing the epidermis from the cutis which was dubbed "corium plastic." In 1953 Spina and Reginato transplanted full thickness skin flaps in the successful repair of three ventral hernias. Using the electric dermatome it is now possible to obtain flaps one-half or three-quarters of the full thickness of the cutis, thus making a corium flap possible The thin epidermal flap is sutured into the wound defect and fixed with a pressure dressing. The most superficial skin layers are not brought in contact with the hernial opening, thus avoiding the possibility of infection.

The corium-epidermis flap has the great advantage over the cutis flap in that rapid epithelization occurs at the donor site. For the best results a three-quarter flap of corium should be used. It is important that the flap be sutured in place with complete tension. Fine silk is used for this purpose. Several cases are outlined by means of sketches illustrating the success of this method of repair. —*Andrew P. Adams, M.D.*

GASTROINTESTINAL TRACT

Prognosis of the Medically Treated Small Gastric Ulcer. NORMAN E. LARSON, JAMES C. CAIN, and LLOYD G. BARTHOLOMEW. *N. England J. M.*, 1961, 264: 330.

CAIN AND CO-WORKERS reported in 1952 the results of medical management as observed after 5 to 11 years in 413 patients with small, apparently benign gastric ulcer. The follow-up period has been extended in the present study to 10 to 19 years in 391 of these cases. Symptomatic relief with healing was obtained in only 105, 26.8 per cent, of the 391 patients. Medical management had been abandoned for surgical treatment because of failure to heal in 158, 40.4 per cent. In 22 of the 158 patients the complication of obstruction, hemorrhage, or perforation had resulted in abrupt termination of medical management. Gastric cancer was found at operation in 37 of the 158 patients. Ulcer symptoms persisted in 105, 26.9 per cent. Death was attributed to gastric cancer in 11, and to the complication of hemorrhage, perforation, or obstruction in 7 of the 105 patients.

Developments in Peptic Ulcer Surgery at the Mayo Clinic. WALTMAN WALTERS. *Arch. Surg.*, 1961, 82: 260.

IN A 6 to 10 year follow-up study of 729 patients with peptic ulcer who underwent the Billroth II operation and 185 who underwent the Billroth I operation, it was found that 92 per cent of the patients who had had the Billroth II type of resection and 88 per cent of those who had had the Billroth I type of resection had excellent or good functional results. The incidence of recurring ulcer was two to three times greater after the Billroth I resection for duodenal ulcer than after the Billroth II resection in both men and women. Only 2 per cent of the patients in each series continued to have severe postgastrectomy symptoms. Regurgitation of bile into the stomach seldom produced symptoms. It was slightly more common in the Billroth II series, but practically never of sufficient severity to require a gastroduodenal anastomosis.

It was not possible to discern a significant difference in the functional results in either men or women when the Billroth I and the Billroth II series were compared. The incidence of recurring ulcer in women was the same as in men after gastroenterostomy plus vagotomy. Recurring ulcer after Billroth II gastric resection for gastric ulcer in women was not noted. Details of the experience with duodenal ulcer, gastric ulcer, and gastrojejunal ulcer are discussed.

The Neutralization Process in Duodenum and Its Influence on the Gastric Emptying in Man. H. O. LAGERLÖF. M.-B. RUDEWALD, and G. PERMAN. *Acta med. scand.*, 1960, 168: 269.

THE PRESENCE of acid in the duodenum is known to delay gastric emptying as well as stimulate the pancreas, liver, and the glands of Brunner. This study was an attempt to correlate the relationship between the motor inhibitory mechanism of the stomach to acid and the alkaline response of duodenal secretions.

Of 31 patients studied 7 had duodenal ulcer, 4 had histamine refractory gastric achylia, 8 had pancreatic achylia, and 11 were normal. A double lumen tube was placed so openings were just above the pylorus and in the region of the duodenojejunal junction. A test solution of tenth-normal hydrochloric acid, sodium chloride, polyethylene glycol, and deuterium oxide was introduced into the stomach. Samples were collected from the jejunum at regular intervals and mixed with glycerol to prevent inactivation of enzymes.

Determinations included *pH*, acidity, titratable alkaline, chlorides, deuterium oxide, polyethylene glycol, bilirubin, amylase, trypsin, and lipase. Mathematical formulas, their derivation, and calculations are given and the results discussed.

The enzyme determinations yielded little information about the total enzyme output because of a high degree of inactivation due to the acid reaction.

Patients with duodenal ulcers had more rapid gastric emptying than normal mainly because of increased uninhibited gastric motility. Those with gastric achylia had less rapid gastric emptying despite a low *p*H evidently because of a reduction in the normal inhibitory effect on gastric emptying promoted by acid in the duodenum. Those with pancreatic achylia did not differ significantly from normal. The role of gastric emptying under a variety of conditions is proportional to the volume of the gastric contents.

Acid stimulation of the duodenum stimulated significant gallbladder emptying in only 2 of 30 persons indicating little cholecystokinin liberation. There was a free continuous flow of liver bile in most subjects. Pancreozymin secretion was little affected by acid stimulation. Amylase, trypsin, and lipase secretion was much the same as with previous secretin tests.

Acid stimulation of the duodenum evoked a secretion of water and bicarbonate which paralleled the rate of emptying with a short time lag. Precise neutralization of duodenal contents occurred in patients with normal, gastric achylia and chronic duodenal ulcers. Those with acute duodenal ulcers and pancreatic achylia had significantly less bicarbonate secretions per emptied amount of acid and higher hydrogen ion concentrations.

If the initial gastric volume and the duodenal *p*H are constant the volume emptied from the stomach is determined by the rate of neutralizing secretion of bicarbonate which in turn is regulated by the uninhibited gastric motility and the sensitivity of the duodenal secretory mechanism to acid.

—*Patrick F. Jewell, M.D.*

Early Postoperative Inflammation of the Efferent Loop After Polya Gastrectomy. F. I. TOVEY. *Lancet*, Lond., 1960, 2: 1209.

THIS IS A REPORT of 3 cases of an early postoperative complication after a Polya type gastrectomy from the surgical section of a hospital in India.

All 3 patients were young males with established duodenal ulcer upon whom a liberal gastric resection with a Bilroth II type reconstruction was performed. The first 2 patients demonstrated difficulty 3 to 4 days after the operation. They were carefully watched but were believed not to have indications for re-exploration and both succumbed. A postmortem examination on both showed extensive inflammation with multiple ulcerations of a 12 to 18 cm. segment of the jejunum just distal to the anastomosis.

The third patient was re-explored fairly promptly after symptoms developed, and a similar pathologic situation was noted. Tubes were inserted both proximally and distally in the jejunum to decompress the inflamed loop and also to enable feeding distal to it; suction of the stomach remnant was continued as well. The bile aspirated from the proximal jejunal tube was boiled and filtered and refed through the distal tube. The patient progressed and recovered.

A plea is made for early re-exploration if there is any significant abdominal pain or restlessness after a gastrectomy, even though there may not be conclusive symptoms of intestinal obstruction or peritonitis. The cause of the condition is unknown.

—*Robert W. Williams, M.D.*

Conservative Treatment or Early Operation in Massive Intestinal Bleeding (Konservative Behandlung oder Fruehoperation bei grossen intestinalen Blutungen). E. WOLLHEIM and K. W. SCHNEIDER. *Deut. med. Wschr.*, 1960, 85: 2169.

A TOTAL of 93 patients were selected for examination within 24 hours of the onset of bleeding. The following conditions were diagnosed clinically or roentgenologically: gastric ulcer in 36 cases, duodenal ulcers in 21, gastritis in 9, duodenal diverticula in 3, esophageal varices in 8, and gastric neoplasms in 8. Of the patients, 61.4 per cent were over 50 years of age.

Blood volume studies conducted as early as possible after hemorrhage demonstrated in 90 per cent of the patients a reduction in red cell mass of over 50 per cent regardless of the cause of bleeding.

Transfusions were kept to a minimum; 12 patients required more than 4 units; the remainder were given between 1 to 2 units of blood. It was shown that plasma was valuable in overcoming tubular insufficiency associated with hemorrhage as well as hemorrhagic and postoperative shock.

The authors stress the importance of maintaining a systolic pressure of at least 90 mm. Hg in conservative therapy, thus winning time for a diagnostic work-up. Because less than 25 per cent of the patients had repeated hemorrhage after admission the authors believe that conservative therapy should be given whenever possible. Advocates of early operative intervention overlook the impossible task of differentiating hemorrhage from ulcer, gastritis, or diverticula, and secondly cannot match the mortality incidence obtained in the conservative management of 56 patients of this series. Only 1 patient died.

—*Andrew P. Adams, M.D.*

Intussusception in Adults. ALVIN M. COTLAR and ISIDORE COHN. *Am. J. Surg.*, 1961, 100: 114.

THE INFREQUENCY of intussusception among adults and the bizarre clinical picture account for the inaccuracy of diagnosis and consequent high mortality. At Charity Hospital, New Orleans, Louisiana, 287 patients with intussusception were seen from 1904 to 1959, of whom 16 per cent were adults. The present report concerns 27 episodes of intussusception in 26 patients over 13 years of age treated at this hospital from 1938 through 1959. This disorder appears more commonly among Caucasians, and men outnumber women 2 to 1. More patients were in the 40 to 49 year old age group than in any other decade. The ileum is the most common anatomic location—ileoileal, ileocolic, and ileocecal in descending order—whereas the colon is a rare site for intussusception.

In 7 of the 27 cases the disorder was idiopathic. In 20 cases, a definite lesion was found, of which 9 were benign neoplasms and 6 were malignant tumors. Preoperatively, the correct diagnosis was made in only 6 of the 27 patients including 1 patient with previous intussusception, 3 with palpable rectal lesions, and 2 with typical barium enema findings. Five interesting case reports illustrate the variety of syndromes and confusing clinical courses which are seen. Often patients were admitted to nonsurgical services and operated upon only after some delay. The chief complaints were abdominal pain, usually colicky, and

vomiting. Pain was usually present for 3 days or less, but had been noted for 1 to 2 weeks in 10 patients and 2 to 8 months in 3 patients. Diarrhea, constipation, and obstipation were infrequent. Rectal bleeding, if bright red, usually indicated an underlying carcinoma. Only 15 patients were acutely ill on admission. Abdominal distention was mild when it was present, but nearly all of the patients had abdominal tenderness.

The operative mortality in this series was 11 per cent, an improvement over earlier reports, and attributed to modern supportive care. However, the presence of gangrenous bowel in 9 of 27 patients emphasizes the necessity of early operation. In cases in which intussusception of the small bowel and right side of the colon is easily reducible, an attempt may be made to decide if the lesion is benign or malignant. If the intussusception is difficult or impossible to reduce, an adequate operation for cancer must be performed, preferably in one stage. Should intussusception of the left side of the colon be present, a defunctionalizing colostomy is recommended so that an adequate resection may be performed at a later time. Lesions of the rectosigmoid and sigmoid colon which cause intussusception are nearly always malignant. A diagnosis of intussusception must be considered by the surgeon whenever an unclear clinical picture and roentgenographic findings are encountered in an adult with confusing abdominal symptoms.

—*Emile L. Meine, Jr., M.D.*

Intestinal Antisepsis and the Spread of Tumors of the Colon. ISIDORE COHN, JR., and M. ATIK. *Am. J. Surg.*, 1961, 100: 3.

BROWN-PEARCE TUMOR was grown in the anterior chamber of the rabbit eye, then removed. The major portion of each tumor was minced and suspended in saline for the bowel experiments. A segment of rabbit colon was isolated and milked clean and the tumor suspension was injected. The colon was divided, then reanastomosed, allowing some spillage. Rabbits were killed from 24 to 59 days after operation for tumor transplantation studies.

There were 37 tumors found in 44 control animals, treated as described. Tumor at the anastomosis was present in 18 rabbits. A second series of studies evaluated the role of intestinal asepsis. Neomycin and tetracycline were instilled after saline flushing of the colon, and the tumor suspension was then injected a before. Of 40 experiments, 37 tumors were found, 29 of these located at the anastomosis. Ten intraluminal tumor ulcerations were found in this group as compared with only 1 in the control group.

A third series of experiments, which included saline irrigation and flushing and manipulation of the colon, simulated the second series, except that no antibiotic was used. Tumor was found later in 16 of 30 anastomoses in this group.

Two additional series of experiments were made to evaluate the antitumor effect of clorpactin XCB. This agent was used to irrigate the peritoneal cavity after the anastomosis, to wash out any tumor cells from the spillage. A paired animal, as a control, received the same amount of saline irrigation only. In 19 paired experiments, tumors were found in 10 saline treated controls and in 16 clorpactin treated animals. Tumors were more massive in the latter group.

These experiments again emphasize that tumor cells can be implanted during an anastomosis of the colon. Tumors were found at the anastomotic line in 50 per cent of all animals used in this study and peritoneal implants in 80 per cent. In these experiments, control of bacterial flora increased the number of tumor implants. There were 78 per cent in the antibiotic treated rabbits and 48 per cent in the controls, a statistically significant difference. Tumors were increased in animals which had reduction in bacteriologic flora by whatever means—antibiotics or saline. Clorpactin did not appear useful in controlling intraperitoneal transplantation of tumor cells. The importance of controlling the spill of tumor cells during open operations of the gastrointestinal tract is therefore re-emphasized. —*Emile L. Meine, Jr., M.D.*

Cancer of the Colon and Rectum. ALVIN L. WATNE, GEORGE E. MOORE, EUGENE BURKE, and KUMAO SAKO. *Am. J. Surg.*, 1961, 100: 7.

THERE ARE 4 main routes of metastasis of carcinomas of the large bowel. These include direct extension, vascular spread, metastasis to regional lymph nodes or via the thoracic duct to the systemic circulation, and by exfoliation into bowel lumen or the peritoneal cavity. Recent investigation of potent anticancer drugs holds promise that circulating tumor cells may be destroyed before they form metastatic implants. The authors have been interested in the vascular and lymphatic dissemination of cells from cancers of the colon and rectum and their exfoliation into the peritoneum. To study this problem, peripheral blood and blood from regional veins was obtained before, during, and after operation. Lymph was drawn from the thoracic duct, and saline irrigations of the peritoneal cavity were obtained and centrifuged. All of these specimens were examined by appropriate techniques for tumor cells. In this study there were 28 patients with carcinomas of the colon on whom "curative" operations were performed; "curative" procedures were carried out on 65 patients with cancer of the rectum; and 12 patients were operated upon who had advanced cancer of the rectum or colon.

Tumor cells were found most often in the regional blood of patients with early carcinoma of the colon and rectum. Such cells were found in regional or peripheral blood of 36 per cent of patients with colon cancer and of 17 per cent of those with rectal tumors. Exfoliation of cells into the peritoneum was related to serosal involvement by the tumor. There was a relationship between the finding of cancer cells in the blood and peritoneum in those patients with carcinoma of the colon but not in those with cancer of the rectum. No blood vessel invasion was seen in the limited areas of colon cancer examined microscopically. Four patients with rectal carcinoma showed blood vessel invasion but no tumor cells were found in their blood. There was no positive correlation between the finding of tumor cells in the blood or peritoneal cavity and tissue invasion or lymph node metastases.

No patient with advanced carcinoma of the colon or rectum had tumor cells in the thoracic duct lymph. Although regional nodes were frequently involved,

these glands may filter cancer cells and prevent their passing further. The vascular route may be more important than others in the causation of pulmonary metastases from colorectal cancer. Accordingly, it appears that each route of spread of cancer cells is relatively independent, and separate measures must be employed for each in the surgical approach to this important cancer problem.

—*Emile L. Meine, Jr., M.D.*

Sacroabdominal Resection for Cancer of the Rectum (Die Chirurgie des Rectum-Carcinoms unter besonderer Berucksichtigung der sacro-abdominellen Rectumexstirpation). H. LAQUA. *Langenbecks Arch. klin. Chir.*, 1960, 294: 552.

THE AUTHOR REPORTS on 1,305 patients with rectal cancers seen at the University of Heidelberg, Heidelberg, Germany from 1943 till 1960. Early in the series the operability rate was 60 per cent; more recently, it has been 80 per cent. There were 672 sacroabdominal resections with an over-all mortality of 11 per cent. In the last 238 cases the mortality has been 8 per cent.

Male patients have an inlying catheter placed and females a vaginal tampon. They are placed in steep Trendelenberg position. The anus is purse-stringed shut. A wide rhombus-shaped incision is made around the anus, dissection is carried up through the levators laterally, and the coccyx is resected. The specimen is mobilized away from the urethra, prostate and bladder, or the uterus, the peritoneum is entered, and the specimen is pushed up into the abdomen. The pelvis is rebuilt beneath the mobilized rectum and the perineal wound is left open after the insertion of two drains.

The patient is then placed supine and the surgeon opens the abdomen, explores it, and cuts across the mesentery of the sigmoid colon at its origin. The mobilized rectosigmoid colon is exteriorized, the wound is closed around the colon, and the colon is not transected till the wound is closed.

This operation is radical where it does the most good, around the tumor-bearing rectum and the perirectal tissue. The incidence of sacral or perineal recurrences has been only 2 per cent. The superior hemorrhoidal lymph drainage system in the sigmoid mesentery is included in the resection. The objection that the venous drainage system should be ligated before the tumor is manipulated might be valid, but the author thinks that the massage of viable tumor cells into the circulation has not been established; nor indeed is the conventional abdominoperineal approach proof against it.

The chief postoperative difficulty was urinary retention and infection; however these can usually be cleared up. Many of the men become impotent, perhaps 60 per cent.

Of 221 patients operated on more than 5 years ago, 61 per cent were alive. The closer the tumor was to the anus, the worse the prognosis—46 per cent of patients alive with tumors less than 7 cm. above the anus and 67 per cent alive with tumors more than 7 cm. above. These figures compare well with results of abdominoperineal resection.

—*William B. Gallagher, M.D.*

LIVER, BILIARY SYSTEM, AND PANCREAS

The Excretion of Radioactive Iodipamide, Cholografin, by Normal and Cirrhotic Males. GUSTAF E. ENGSTROM, JOSEPH L. RABINOWITZ, HERBERT D. STRAUSS, GEORGE T. WOHL, and RALPH M. MYERSON. *Am. J. Roentg.*, 1961, 85: 119.

BY MEANS OF cholografin, iodipamide, labelled with I^{131}, the rate of excretion and the total excretion of the material in the urine was measured in 37 male patients, of whom 22 had normal hepatic function and 15 impaired function due to cirrhosis. With few exceptions the cirrhotics excreted a larger percentage of the contrast material in the urine in 24 hours and at a more rapid rate than the normal patients. There was detectable radioactivity over the thyroid gland in all patients studied. Counting the blood samples and external counting over the liver failed to differentiate between the two groups.

The findings substantiate previous observations that in the presence of chronic hepatic disease the contrast medium is excreted through the kidneys rather than through the liver and biliary passages.

—*Lois Cowan Collins, M.D.*

Biliary Cystadenomas and Polycystic Disease of the Liver (Cystadénomes biliaires et maladie polykystique du foie). M. COURTOIS-SUFFIT and H. CHARLEUX. *Sem. hôp. Par.*, 1960, 36: 3408.

THE AUTHORS use the term "biliary cystadenoma" synonymously with that of solitary biliary cysts of the liver. They state that these solitary cysts are related to polycystic disease of the liver as far as the cause is concerned and that intermediate forms are usual rather than exceptional. Their theory is well exemplified by 4 case reports. The first patient was a 75 year old woman with vomiting and a mass in the epigastrium. On surgical exploration a large cyst of the left lobe of the liver was found. This cyst was surrounded by numerous tiny cysts. The second case was that of a 61 year old woman with hepatomegaly. Abdominal exploration revealed a large cyst involving the right lobe of the liver. The third case was that of a 66 year old woman with a clinical picture of acute cholecystitis. At exploratory laparotomy, polycystic disease of both lobes of the liver was found. The fourth patient, a 63 year old woman, was found to have a mass in the epigastrium during physical examination. On surgical exploration, polycystic disease of the liver was found. In addition, the third and fourth patients also had polycystic disease of the kidneys. A review of the literature follows these presentations. Signs and symptoms are also discussed. No original contribution is presented. The authors do not recommend any treatment for the polycystic disease. In the case of solitary cysts, excision is occasionally possible, especially if they are pedunculated. Marsupialization and drainage are otherwise preferred. —*Joseph J. Bahuth, M.D.*

The Sphincter of Oddi and Gallbladder Function—I, Preservation of Function After Section and Resection of the Sphincter. ROBERT E. LEMPKE. *Ann. Surg.*, 1960, 152: 815.

EIGHT CONSECUTIVE PATIENTS in whom the sphincter of Oddi was sectioned or resected without prior or

concomitant cholecystectomy are the subject of this report from the Veterans Administration Hospital and Indiana University Medical Center, Indianapolis, Indiana. Contrary to what might be expected on the basis of experimental work in dogs, all patients were shown to have a functioning gallbladder, as determined by oral cholecystography during the postoperative period.

A possible explanation for continued filling of the gallbladder after destruction of the sphincter of Oddi is that the resistance to bile flow necessary to produce distention of the gallbladder is maintained by the duodenal musculature. This component of the sphincteric mechanism is of such magnitude that it can probably perform this function by itself. However, the possibility that sphincteric action was re-established as a result of healing has not been excluded.

The intact duodenal musculature also prevents reflux of duodenal contents into the common duct and apparently prevents the development of inflammatory complications of the biliary tract in man. Incompetence of the choledochoduodenal junction attributable to an extensive sphincterotomy was demonstrated in 2 patients. One patient who originally had a diffuse, sclerosing inflammation of the biliary tract was found to have chronic cholecystitis when an operation was performed 2 years later for partial obstruction of the common duct by biliary sediment. The other patient has not demonstrated any evidence of this complication over a much shorter period of observation.

The evidence from observation of these 8 patients is not sufficient to permit the conclusion that the gallbladder should not be removed when the sphincter of Oddi is sectioned or resected. The observations are of interest in that they reveal the presence of many unanswered questions regarding the action of the sphincter of Oddi in gallbladder function in man.

—Stephen W. Carveth, M.D.

Iron Secretions in the Bile During Drainage of the Common Duct After Oral and Intravenous Administration of Iron (Die Eisenausscheidung im Gallensaft bei Choledochusdraenage nach oraler und intravenoeser Belastung). W. WEHNER and H. WOLFF. *Zbl. Chir.*, 1960, 85: 1997.

NORMALLY, the body preserves iron very well; only about 8 mgm. per day are lost in stool and urine. Hemorrhages, some diseases, and pregnancy are known to cause great losses. The liver is considered the central organ for iron metabolism. In dogs, only 0.1 to 0.4 mgm. of iron were found in 24 hour bile specimens. The iron in the stool can be iron from unresorbed food, or that excreted by the intestinal mucosa, or can come from the various fluids of the digestive juices. Bile is an important part of the latter. This is of interest, since, after common duct explorations, the bile is usually drained and lost by a T drain. This could mean an iron loss in addition to the blood loss during the operation. Patients with a T drainage offer the possibility to study the effect of oral and parenterally administered iron upon its excretion in bile.

Fourteen patients, 7 with icterus, were used in the experiment. Only 2 patients had a normal serum bilirubin level. The average age of the patients was 57.7 years. All the other laboratory results are given. In the oral test, 1.5 mgm. of iron/kgm. body weight and in the parenteral test, 1.0 mgm. iron/kgm. body weight were given. After evaluation of all the shortcomings of the methods used, the authors conclude that only the parenteral administration resulted in a transient significant rise of iron in the bile. The concentration, however, is still so low that only 1 per cent of the amount administered is excreted. The effect of iron therapy is not, therefore, endangered.

—Eckhard Fischer, M.D.

Gallstones in an Autopsy Series. ANSGAR TORVIK and BJØRN HØIVIK. *Acta chir. scand.*, 1960, 120: 168.

IN A 6 YEAR PERIOD from 1952 to 1957 the total number of deaths in Oslo, Norway was 24,918. During that same period 11,129 autopsies were performed at the Department of Pathology at the Ulleval Hospital in that city. This represents 45 per cent of all deaths in Oslo. It is from this autopsy study that this analysis is made. Among the 11,129 autopsies there were 2,020 cadavers with calculi in the gallbladder, cystic duct, or common duct. In addition, there were 155 postmortem studies of bodies of patients who had had cholecystectomy, presumably for cholelithiasis. The total number of instances of gallstones in this series, therefore, is probably 2,175, a total incidence of 19.5 per cent. The incidence in the male autopsy group was 12.7 per cent and in the female group 27.1 per cent. No gallstones were found in cadavers less than 20 years of age. In a study of the different age groups it was noted that a significant incidence did not appear until the decade between 40 and 49 years of age and from then on showed an even and progressive increase in each decade up to 90 to 100 years, at which age the incidence was 32.9 per cent. The age incidence graphs show a similar curve for both male and female where the formation of gallstones appears to start at the same time in both sexes.

Sixty-four patients had died from biliary or hepatic complications caused by the gallstones and in 3 additional cases the gallbladder disease contributed significantly to death. There were 39 cases of unquestionable carcinoma of the gallbladder. Seven other cases of extensive carcinomas were probably primary gallbladder tumors. So the incidence of gallbladder carcinomas was 0.35 or 0.41 per cent of all cases or 1.8 to 2.1 per cent of all cases with cholelithiasis.

The incidence of carcinoma of the gallbladder was much higher in females. Thirty-six of the 39 positive cases were in females. Only 4 of the cadavers with gallbladder carcinoma were less than 60 years of age. Calculi were present in 34 of the 39 with unquestionable gallbladder carcinoma, an incidence of 87 per cent.

The frequency of carcinomas in cases of gallstones is relatively low, 1.8 to 2.1 per cent. In the instances of carcinoma of the gallbladder there had been only a short history of gallbladder symptoms. A modest number had had symptoms for more than a year. In the majority there had been a clinical history of 2 to 3 weeks before admission to the hospital.

—Ward D. O'Sullivan, M.D.

Leiomyosarcoma of the Gallbladder (Su di un caso di leiomiosarcoma della colecisti). R. Dello Russo and L. Paladino. *Riforma med.*, 1960, 74: 1309.

Leiomyosarcoma of the gallbladder is an extremely rare condition and only 6 cases have been described in the literature to date. This article is a case report of 1 patient who had this disease and was treated surgically.

The patient, a 64 year old man, was admitted to the Department of Surgery of the University of Naples Medical School, Italy with a 2 month history of intermittent fever spiking to 39 degrees C associated with moderate, continuous, dragging pain over the right upper quadrant without radiation. Occasional biliary vomiting was also noted. No jaundice was ever observed. The past history was noncontributory. On physical examination the patient appeared in fair general condition. Guarding was present over the right upper quadrant. By deep palpation a mass was felt under the inferior margin of the liver. The liver was moderately enlarged. The rest of the physical examination was negative. Liver function tests gave the following results: Takata-Ucko 2 plus; McLagan 4 thymol units; Wunderly and Van den Berg negative. Needle puncture of the mass was performed and a small amount of cloudy, yellowish fluid was obtained which was negative for tumor cells. Roentgenographic studies of the biliary tract failed to result in visualization of the gallbladder and the biliary tree. Operation was performed and the gallbladder appeared to be enlarged and adherent to the colon and duodenum. A hard mass was present on its fundus and it was adherent to the choledochus. The gallbladder was removed together with a small portion of the surrounding hepatic parenchyma. At gross examination the gallbladder wall appeared markedly altered; its thickness averaged 3 to 4 cm. Several necrotic areas were present and the mucous membrane was almost totally replaced by the neoplastic tissue and hemorrhagic infiltrations. Histologic examination revealed the presence of the following elements: (1) small, markedly immature cells with basophilic nuclei; (2) more mature elements with basophilic nuclei and granular basophilic cytoplasm considered as atypical myoblasts; (3) cells with large, fusiform or multilobar basophilic nuclei and abundant cytoplasm; and (4) granular cells of Abrikond. The histologic diagnosis was leiomyosarcoma derived from the cellular elements of the arteriolar wall.

—*Riccardo Benvenuto, M.D.*

SURGERY OF THE FEMALE REPRODUCTIVE SYSTEM

UTERUS AND ADNEXA

Postmenopausal Endometrial Tuberculosis. E. M. BARBOUR. *J. Obst. Gyn. Brit. Empire*, 1960, 67: 1008.

TUBERCULOUS ENDOMETRITIS first diagnosed in the postmenopausal patient is an unusual, even rare, finding. The author reviews the clinical and pathologic material obtained from 9 such patients found in 30 years at the Royal Samaritan Hospital, Glasgow, Scotland.

Seven of the 9 patients were parous, indicating that the disease was contracted late in life. Further confirmation was the fact that no patient had a previously abnormal menstrual pattern. No patient had caseation, ulceration, or pyometra. All 9 showed patchy, small tubercles best diagnosed by histologic pattern alone.

There is a brief review of other reports on this subject.

—M. Leon Tancer, M.D.

Colposcopy and Schiller's Iodine Test as an Aid in the Diagnosis of Malignant and Premalignant Lesions of the Squamous Epithelium of the Cervix Uteri. RUNE NYBERG, BO TÖRNBERG, and BJÖRN WESTIN. *Acta obst. gyn. scand.*, 1960, 39: 540.

THE AUTHORS describe in detail the nomenclature of colposcopy and its use in diagnosis and advise its use in Sweden in spite of the present controversy. On a selected series of 316 patients a gynecologic examination with the Schiller test and colposcopy was performed and one biopsy specimen was removed from one colposcopically defined area. All patients had some cervical changes other than strongly suspected or confirmed malignant lesions, but neither these symptoms nor the patients' age gave a clue as to possible atypia or early cancer.

Macroscopic inspection was worthless in this differentiation, whereas the Schiller test as well as colposcopy allowed identification of atypia, especially when a sharp border of an iodine-negative area was seen. Columnar epithelium can be identified with certainty by colposcopy, and squamous epithelium with both methods. If the colposcopic picture was benign and the Schiller test produced dark stain, no histologic atypia was ever seen. Significant atypical epithelium or malignant disease was present in 26 per cent of the patients in whom atypical colposcopic pictures had been obtained.

—W. Dieter Bergman, M.D.

Combined Radiologic-Surgical Therapy of Stage I or II Carcinoma of the Uterine Cervix. EDWARD J. CRAWFORD, JR., LEWIS S. ROBINSON, LLOYD A. HORNBUCKLE, and WILLIAM E. GODFREY. *Am. J. Obst.*, 1961, 81: 148.

DATA ARE PRESENTED from the Confederate Memorial Medical Center, Shreveport, Louisiana on 105 patients with stage I or stage II carcinoma of the cervix treated first with full therapeutic irradiation and 6 weeks later with radical hysterectomy and bilateral pelvic lymphadenectomy. Of the 48 patients treated 5 or more years ago, 79.2 per cent are alive and apparently free of disease.

Residual carcinoma was found to be present in 21.9 per cent of the 105 patients. Fifty-six and five-tenths per cent of the patients with residual carcinoma are now alive and apparently free of disease.

There has been 1 operative death, a primary surgical mortality of 1 per cent. In addition, 1 patient died of intestinal obstruction 6 months after operation.

The most common complications are those involving the genitourinary tract. Thirty-two patients had hydronephrosis which resolved spontaneously in 25. There was 1 urinary fistula, vesicovaginal. There were 4 bowel fistulas.

Although the results obtained so far are favorable enough to justify continued evaluation, more time must elapse before the combined roentgenologic and surgical approach can be assigned its proper role in the treatment of carcinoma of the cervix.

—Alan Rubin, M.D.

Results of Bilateral Ovarian Wedge Resection. W. P. PLATE. *Gynaecologia*, Basel, 1960, 150: 267.

THE REASONS for the success of ovarian wedge resection in the treatment of the Stein-Leventhal syndrome are unknown. Some investigators think that removal of ovarian tissue permits a given amount of gonadotropin to act on a lesser ovarian residue and hence to have a greater effect, causing ovulation. Others believe that excessive thecal tissue has been removed with the same result.

The author reports a series of 120 wedge resections. Those performed solely to cure hirsutism were unsuccessful and this indication has been abandoned. One hundred and sixteen wedge resections were performed in order to institute regular ovulatory cycles, and follow-up was accomplished in 111 cases, the subject of this report. Wedge resection was not performed if gonadotropin and estrogen levels were abnormal or if 17-ketosteroids were more than slightly increased. It was not necessary for ovaries to be clinically palpable.

Of 93 patients who had never been shown to have an ovulatory cycle, 51 per cent were successfully treated. Of 62 patients whose primary complaint was infertility caused by anovulation, 32 per cent were successfully treated. The author stresses the fact that greatest success, approaching 50 per cent, was accomplished in those patients with anovulatory menstruation or secondary amenorrhea.

—M. Leon Tancer, M.D.

Clinical Aspects of Metastatic Ovarian Cancer of Extragenital Origin. HARALD JOHANSSON. *Acta obst. gyn. scand.*, 1960, 39: 681.

THE CASES OF 79 patients with metastatic ovarian tumors of extragenital origin seen at the Radiumhemmet, Stockholm, Sweden between January 1930 and March 1959 were selected for study because of an

admitting diagnosis of ovarian tumor. Ovaries removed from patients with cancer of the breast and subsequently found to contain metastatic cancer were excluded.

The site of the primary tumor was the gastrointestinal tract in 84 per cent of the cases: stomach in 31 cases, colon in 19, and the sigmoid and rectum in 16; and the breast in 14 per cent, 11 cases. The pancreas and the kidney accounted for 1 case each. Contrary to other reports, 82 per cent of patients, including all those with breast cancer, were over 40 years old.

Metastatic ovarian cancer can appear as large bilateral ovarian tumors with a silent primary lesion or may not be discovered until several years after removal of the primary tumor. One of the patients with breast cancer, 22 of those with gastric cancers, and 8 of the patients with intestinal cancer had their primary lesions discovered after removal of the metastatic ovarian tumors. As a rule, this was within 3 months. Forty-seven of the patients in this study had the secondary ovarian tumor diagnosed and treated after resection of the primary cancer, in 3 of the patients with breast cancer at 9, 11, and 16 years after mastectomy.

Although most of the patients died within 1 year after resection of the ovaries, 10 of the 79 are still alive. These consist of 4 with gastric cancer, 4 with colon or rectal cancer, 1 with breast cancer, and the 1 patient with renal cancer. One patient with cancer of the stomach and 1 with cancer of the colon have survived 6 years after oophorectomy and are reported in detail.

The author recommends that at the time of resection of gastric or intestinal cancer in women over 40 years of age surgical castration also be performed. Oophorectomy should also be considered for women over 40 years old who have breast cancer.

—James J. Monge, M.D.

PREGNANCY AND COMPLICATIONS

Use of Relaxin During Parturition. Robert E. L. Nesbitt, Jr., and George Cirigliano. *N. York State J. M.*, 1961, 61: 90.

The use of relaxin in clinical obstetrics has aroused considerable controversy. A number of biologic effects of the hormone have been well established and include conditioning of the pregnant uterus to oxytocin, increased dilatability of the rat cervix, alteration of uterine and cervical weight, suppression of spontaneous uterine motility, softening of the uterine cervix, and preparation for a placental detachment. All of these observations have been made in various animal strains, but none has been confirmed in the human. These observations have led to a number of potential uses of the hormone in clinical obstetrics and gynecology such as the treatment of dysmenorrhea, prevention and treatment of abortion, prevention and treatment of premature labor, treatment of rigid cervix, and induction of labor.

The current study concerns only the effect of relaxin on the duration of labor. It is difficult to understand how relaxin can be of any particular value in the management of prolonged labor or induction of labor, since in animals the hormone must be given in large doses and results are not apparent for several days. Furthermore, softening of the cervix is a minor factor in prolonged labor so that even if the hormone did work, its applicability would be extremely limited. Relaxin was administered to 102 normal parturient women in spontaneous labor and selected at random from the clinic population. The patients received 40 mgm. of relaxin or a placebo in a double-blind study, all observations being made by a single observer. The length of labor was not shortened by the administration of relaxin and, in fact, seemed slightly but not significantly longer. The incidence of required forceps delivery was the same whether the patient received the relaxin or the placebo. As a result of these observations, the authors concluded that under the circumstances of the experiment, relaxin was of no value in shortening the duration of labor.

—James F. Donnelly, M.D.

Jaundice in Pregnancy. Bernard Samuels. *Obst. Gyn.*, 1961, 17: 103.

Jaundice is infrequently associated with pregnancy, the incidence varying from 0.7 to 0.02 per cent. The commonest causes are infectious hepatitis, serum hepatitis, sickle-cell anemia and related hemoglobin disease, acute fatty metamorphosis (acute yellow atrophy), cirrhosis of the liver, hemolytic anemias, cholelithiasis, hyperemesis gravidarum, and Weil's disease.

The experience with this syndrome at an infirmary over a 10 year period, 1950 to 1959, is presented. The incidence was .04 per cent. There were 6 patients with infectious hepatitis, 1 with thorazine hepatitis, and 1 with jaundice due to a gall stone that obstructed the common bile duct. Jaundice became manifest during the first trimester in 2 patients, during the second trimester in 3, and at term in 3.

Diagnosis is frequently difficult. A thorough history is important. Information concerning diet, alcoholic intake, food intolerances, "indigestion," pain, nausea, vomiting, diarrhea, and color of stools and urine should be taken. Exposure to toxins or infectious disease, especially hepatitis or mononucleosis, is important. The patient should be questioned about transfusions, injections, and the use of hepatoxic drugs.

The important points to observe on physical examination are the severity of jaundice, presence of anemia, prominent venous collateral circulation, spider angiomas, cachexia, lymphadenopathy, splenomegaly, and ascites.

Laboratory tests recommended are: (1) hepatic excretory function including direct and indirect bilirubin, serum alkaline phosphatase, total serum cholesterol, and bilirubinuria; (2) parenchymal liver damage by noting alterations in the serum proteins, cephalin flocculation test, thymol turbidity test, and serum transaminase; (3) specific metabolic functions, i.e., urine urobilinogen and plasma prothrombin; and (4) search for extrahepatic conditions that may produce jaundice, i.e., slide test for Weil's disease, heterophile agglutination, red cell osmotic fragility test, and malaria smear.

The management of a pregnant patient with jaundice depends on whether medical or surgical

jaundice is present. Nothing must be done that will aggravate an already embarrassed liver.

Specific drugs or operation should be used when indicated. Vitamin K is indicated if the prothrombin time is abnormal, especially at delivery to prevent postpartum hemorrhage. Corticosteroids and antibiotics may be necessary in certain severe cases. Definitely indicated gallbladder operations or roentgenologic studies may be performed during pregnancy. Careful supervision during pregnancy, delivery, and the postpartum period is mandatory.

No case of abortion, intrauterine death, or fetal anomaly directly attributable to hepatitis occurred. No maternal deaths were reported in this series of patients. One patient had postpartum hemorrhage and there were no other complications of delivery or the puerperium. —*Harry Fields, M.D.*

A Comparison Study of Antihypertensive Drug Therapy and the Modified Stroganoff Method in the Management of Severe Toxemia of Pregnancy. VERN N. WALKER and WILLIAM S. BAKER, JR. *Am. J. Obst.*, 1961, 81: 16.

DURING THE 3 year period from 1 July 1953, to 30 June 1956, a total of 13,771 patients were delivered at the U.S. Naval Hospital, San Diego, California. Of this number, 693 cases or 5.03 per cent were coded as showing a variant of toxemia of pregnancy according to the Joint Armed Forces Statistical Classification and Basic Diagnostic Nomenclature of Disease and Injuries of 1949. All charts were reviewed and data compiled on special analysis sheets devised for the study.

The Definition and Classification of Toxemias of Pregnancy, as established by the American Committee on Maternal Welfare, 1 April 1952, was strictly adhered to in this study. Cases classified as toxemia purely on the basis of excessive weight gain without the presence of other diagnostic signs were not included. Those patients manifesting only transient antepartum, intrapartum, or postpartum elevations of blood pressure of less than 6 hours' duration were likewise excluded. Cases of confirmed hypertensive disease in the pregnancy state were not included unless definite substantiated superimposed toxemia developed.

From an analysis of the cases the following conclusions were made: Toxemia is found most frequently in the younger primigravidas. Excessive weight gain noted in this study, although possibly a precursor of toxemia, was not directly related to the severity of the disease process. Although toxemia by definition is manifested by the appearance of symptoms during or after the twenty-fourth week of gestation, the majority of cases occurred during or after the thirty-fifth week.

The use of antihypertensive medications in the treatment of toxemia of pregnancy significantly decreases arteriolar vasospasm as reflected by the eye ground findings and the fall of the blood pressure to near normotensive levels. Antihypertensive treatment of toxemia eliminates the need for cesarean section as a means of terminating a pregnancy except for purely obstetric indications. The use of antihypertensive medications significantly reduces the interim time required for the return of blood pressure to safe and normotensive levels. When antihypertensive medications were used in the treatment of toxemia an apparent decrease in stillbirths was noted. Treatment of toxemia with antihypertensive drugs did not significantly decrease the combined incidence of fetal and neonatal mortality in this study. Maternal morbidity and mortality rates were significantly decreased in the group treated with antihypertensive medications in the management of severe toxemia of pregnancy. —*Charles Baron, M.D.*

The Operation of Choice for Ectopic Pregnancy with Reference to Subsequent Fertility. ALLAN VEHASKARI. *Acta obst. gyn. scand.*, 1960, 39: Suppl. 3.

THE PRIMARY AIM of surgical therapy in ectopic pregnancy is preservation of life. In recent years through the means of blood banks, improved anesthesia, and antibiotics, operative mortality and morbidity have been greatly reduced. Thus it would appear that a secondary aim, namely, preservation of reproductive capacity, might legitimately be pursued.

Three hundred and sixty-six patients with ectopic pregnancy were treated by surgery from 1948 to 1958 at Oulu County Hospital, Finland. A sterilizing procedure was performed in 22 or 6 per cent of the cases. A conservative operation, sparing both tubes or the sole remaining pregnant tube, was performed when tubal abortion occurred in 31 or 8.5 per cent of the cases. The contralateral tube was preserved—even restored if necessary—in 313 or 85.5 per cent of cases.

Postoperative fertility in those patients who had nonsterilizing operations and were able to be followed up was achieved in 148 of 307 or 48.2 per cent, and there were 276 pregnancies in this group of 148 patients. Among these pregnancies were 173 deliveries, 62.7 per cent, and 33 ectopic pregnancies, 11.9 per cent. One patient had 5 full term pregnancies after her initial operation.

The procedures used to preserve fertility included salpingolysis or salpingostomy of the contralateral tube, amputation of the affected tube, expression of the ovum, or evacuation of a hematocele. None of these procedures was shown to increase morbidity or mortality.

Postoperative pregnancies occurred equally as often in patients who had reconstructive surgery as in those patients who had homolateral salpingectomy and normal contralateral tubes. Thus it would appear that an effort towards such reconstructive surgery in younger women is definitely worth the effort involved.

However, 32 patients had a subsequent ectopic pregnancy and the incidence among patients who had reconstructive surgery as opposed to those with normal contralateral tubes was about 2 to 1. Since the occurrence of the repeated ectopic pregnancy represents a risk, a reconstructive procedure should be performed only when postoperative fertility is clearly desirable.

The author concludes that in cases of tubal pregnancy in women past 40, future fertility may be ignored; that in younger women with normal contralateral tubes, homolateral salpingectomy is the procedure of choice; and that in young women with a clear need for preservation of fertility in whom contralateral adnexal changes justify a diagnosis of

tubal sterility, preservation of the homolateral tube and reconstructive surgery of the contralateral tube is advisable. —*M. Leon Tancer, M.D.*

LABOR AND COMPLICATIONS

Further Observations on the Safety of the Pitocin Drip. T. J. RYAN. *J. Obst. Gyn. Brit. Empire*, 1960, 67: 962.

IN A PREVIOUS ARTICLE, 323 patients were analyzed with regard to the results obtained with the pitocin drip for the induction of labor. This report describes its use in another 327 patients. This series consisted of two groups.

Group A was comprised of patients in whom the onset of labor was delayed more than 24 hours after rupture of the membranes. There were 227 patients of whom 90 were primigravidas and 137 multiparas. The duration of pregnancy varied from 18 weeks in 1 patient to more than 40 weeks in 101 patients. One quarter ml. or 2.5 units of pitocin was thoroughly mixed with 1 bottle, 540 ml. of dextrose, dextrose in saline, or normal saline and the drip was started and run at the rate of approximately 40 drops per minute. Supervision of the patient was not constant, the patient being seen only as often as 1 in normal labor.

Results in this group revealed that 214 patients or 94 per cent were delivered within 36 hours of the commencement of the drip, the average time between commencement of the drip and the establishment of labor—the latent period—being 1.5 hours for multiparas and 3 hours for primigravidas. Thirteen patients in this group required cesarean section for delivery. Of 228 infants 10 were stillborn and 4 died neonatally. Only 1 of the stillbirths was due to the pitocin drip.

The second group consisted of 100 patients in whom induction of labor was deemed advisable because of obstetric complications. The complications included eclampsia, severe pre-eclampsia, concealed accidental hemorrhage, unstable lie, minor degrees of placenta previa, intrauterine death, and meconium staining in the liquor as revealed at artificial rupture of the membranes. In these patients artificial rupture of the membranes was performed and followed immediately after by a pitocin drip. There were 66 multiparas and 34 primigravidas in this group. The duration of gestation varied from 18 weeks in 1 patient to more than 40 weeks in 19 patients.

Ninety-six of the patients or 96 per cent were delivered in 36 hours, the average latent period being 2 hours for multiparas and 1 hour and 40 minutes for primigravidas. The average length of labor was 5 hours 40 minutes for multiparas and 11 hours 5 minutes for primigravidas. Four in this group required cesarean section.

Of the 97 infants delivered vaginally, 14 were stillborn and 5 died neonatally. Of the stillbirths, 9 were dead before induction was started, 3 were abnormal babies, 1 was the result of a badly executed breech delivery, and 1 was a 3 pound baby delivered to a mother with severe toxemia.

Of those who died neonatally, 1 died during exchange transfusion, 1 weighing 4 pounds 11 ounces born to a mother with placenta previa died at 7 hours, and the other 3 were born to mothers with severe pre-eclampsia.

The author believes that constant supervision of patients receiving the pitocin drip is unnecessary and time consuming. The drip is considered safe in any patient for whom induction of labor seems necessary. This has been used by the author in the following conditions: pre-eclampsia and essential hypertension, disproportion, previous caesarean section, elderly primigravidas, grand multiparas, concealed accidental hemorrhage, eclampsia, twin pregnancy, unstable lie, multiparas who had no previous living children, meconium-stained liquor, and 1 patient in whom the fetal heart was irregular before the membranes were ruptured. —*Harry Fields, M.D.*

SURGERY OF THE MALE REPRODUCTIVE SYSTEM

PROSTATE AND SEMINAL VESICLES

The Association of Stones in the Upper Urinary Tract with Prostatic Calculi. MILES FOX. *Brit. J. Urol.*, 1960, 32: 458.

AN ASSOCIATION between stones in the prostate gland and in the urinary tract has been reported previously. To obtain a wider perspective on a study of prostatic calculi and to correlate associated clinical conditions, all roentgenograms of 3,510 men attending one hospital over a 5 year period were examined. The average age was 56 years. Four hundred and eighty-four of the patients had prostatic stones. Since there were stones not sufficiently enlarged to be roentgenographically visible the incidence was undoubtedly greater.

The condition most commonly associated with prostatic calculi was benign prostatic enlargement which had occurred in 54.5 per cent. Prostatitis was present in 8.5 per cent. Stones in the kidneys and ureter, excluding patients with prostatic enlargement and urinary tract infection, were present in 51 patients or 10.5 per cent. Stones in the bladder, with 85 per cent of these patients also having prostatic enlargement, were noted in 5 per cent.

A special study was made of the 51 patients in whom there were both urinary tract and prostatic calculi without infection or prostatic enlargement. The average age incidence in this association of calculi was 43 years as compared with 56 years in the whole series with prostatic calculi. The younger age groups had a higher rate of association. Thus, 50 per cent of patients under 25 years of age with prostatic stones also had upper urinary tract calculi, implying the significance of findings of prostatic calculi in healthy young adults. By analysis, most of the upper tract calculi were mixtures of calcium oxalate and phosphates.

Studies of calcium metabolism revealed a high incidence of hypercalciuria. Prostatic calculi originate and lie within the ducts and acini possibly because of urinary reflux into the distal ducts and stasis with predisposing hypercalciuria. The high concentration of calcium in prostatic fluid may also cause a precipitation of "free" calcium in a urine with low citrate content. This is also a problem worth investigating.

—Allan K. Swersie, M.D.

Studies on Fluid and Electrolyte Alterations During Transurethral Prostatectomy. FRANK E. CECCARELLI and LOUIS K. MANTELL. *J. Urol.*, Balt., 1961, 85: 75.

AS TRANSURETHRAL PROSTATECTOMY becomes more and more popular and is more frequently utilized by urologists to remove the adenomatous prostate, knowledge of the physiology involved should be increased.

The authors carefully studied 34 patients who underwent a transurethral prostatectomy. There was a decrease in the circulating plasma volume and in extracellular sodium although an absolute loss of sodium from the body was not inferred. An increase in weight and hematocrit was demonstrated and apparently the length of time utilized for resection and the amount of tissue resected were not factors in these changes.

The TUR reaction syndrome is not dependent upon hemolysis and may be present with normal, elevated, or depressed blood pressure. Prevention is comparatively simple. The irrigating solution should be under as little pressure as possible and should be nonhemolytic. The venous sinuses ideally should not be opened, and the time of resection should be limited to 60 minutes if feasible.

The authors believe that the patients with a TUR reaction have changes grossly similar to those of water intoxication in that there is apparently a pick-up of the isotonic, hyposmotic irrigating fluid. This locates in the extravascular space causing a loss of sodium and a decrease in the circulating plasma volume. Hypertonic saline is generally adequate to permit a shift of fluid and help osmotic diuresis as well as chronic hyponatremia.

—John R. Herman, M.D.

Prostatectomy—Transcapsular or Transvesical. B. ANDERSEN and J. THYSSEN. *Acta chir. scand.*, 1960, 120: 188.

THE AUTHORS compared 99 transcapsular and 90 transvesical prostatectomies. Particular stress was laid on the duration of postoperative bleeding, oozing of urine through the wound, and the length of stay in the hospital after the operation. In the transcapsular operation a transverse incision was made approximately over the middle of the prostatic capsule and digital enucleation of the adenomas and closure of the capsule with continuous chromic catgut sutures were carried out. The transvesical procedure was initiated by a small incision into the anterior wall of the bladder followed by digital enucleation of the adenomas.

The two groups compared favorably concerning age distribution, duration of symptoms, and weight of removed adenomas. A particularly striking difference is found in the length of stay in the hospital after the operation. On the tenth day 34 per cent of the patients who had undergone transvesical prostatectomy had been discharged as compared with 14 per cent of those who had undergone transcapsular prostatectomy. Fifty per cent of those with the transvesical operation had been discharged on the twelfth day as compared with the seventeenth day for the transcapsular operation. The average postoperative stay was 16.4 days for the transvesical operation and 18.1 days for the transcapsular operation. Disregarding epididymitis, complications occurred in 17 per cent after transcapsular and in 18 per cent after transvesical operation.

In respect to the duration of postoperative bleeding, oozing of urine through the wound, and duration of postoperative stay in the hospital, the transvesical method was superior to the transcapsular. A study on the significance of the duration of postoperative catheterization was reported. This concerned only the transvesical group of 90 patients which was divided into two subgroups of 39 and 51 patients. In the sub-

group of 39 patients the catheter was removed as soon as the urine became clear and the oozing of urine through the wound had practically ceased. As a rule the suprapubic catheter was removed on the first or second day and the urethral catheter on the fourth to the tenth day. In the group of 51 patients, the suprapubic catheter was removed on the first day after operation and the urethral catheter on the second or at the latest on the third day, regardless of whether the urine had become clear or the oozing of urine through the wound had ceased. The difference between the subgroups whose postoperative catheterization differed indicates that this technical detail, i.e., early removal of the catheters, is of essential importance to the postoperative course. —*Ray C. Johnston, M.D.*

Blood Loss in Prostatic Surgery. A. W. Bruce, J. Zorab, and B. Still. *Brit. J. Urol.*, 1960, 32: 422.

Ninety-two unselected patients on whom retropubic prostatectomy was performed were studied from the point of view of blood loss in two groups: controlled hypotension and uninfluenced normotensive patients. The technique of anesthesia was comparable in the two groups and in all patients, the only difference being the use of hexamethonium bromide or pentolinium tartrate for controlled hypotension. In the latter group the systolic blood pressure was dropped to 60 mm. Hg and maintained at this level until closure of the prostatic capsule. Within 3 hours the blood pressure usually returned to normal in the controlled hypotensive group.

Careful measurements of blood loss by weighing the swabs and measurement of the bladder washouts in both groups indicated that the total blood loss is about double the amount lost at operation, and the patients in the normotensive group lost about three times as much blood as those in the hypotensive group. Controlled hypotension reduces blood loss not only during the operation but also in the postoperative period. No patient in the hypotensive group received a transfusion during the operative procedure whereas one-third of those in the normotensive group did.

There was some reduction in the postoperative stay in the hypotensive group but no significant differences in complications were noted. There is, however, a considerable reduction in the amount of blood necessary during the operative procedure and after operation when the procedure is performed under hypotensive conditions rather than under normotensive conditions. Neither the weight of the prostate gland removed nor the age of the patient appeared to have any influence on the amount of blood lost. Controlled hypotension does seem to improve operating conditions and facilitates hemostasis. One thing is certain, there is a reduction in the need for replacement transfusion and its associated risk. The benefits, however, must be considered in relation to the risk inherent in the hypotensive procedure, although in this series no complications attributable to the lowered blood pressure occurred. —*Peter L. Scardino, M.D.*

SCROTUM AND TESTES

Testicular Tumors. R. E. Reinhard and A. R. W. Climie. *Harper Hosp. Bull.*, Detr., 1960, 18: 302.

A review is made with special reference to clinical history, histopathology, and follow-up of 32 patients with testicular tumors admitted to a 650 bed hospital in a 12 year period.

There were 2 nongerminal tumors, an interstitial cell type and a tumor of the rete testis in a 2 year old boy, described in detail. Among the germinal types the seminomas were by far the most common with 19 cases and occurred in a relatively older age group. In this group, too, the average duration of symptoms prior to diagnosis was longest—10 months. Other germinal types are classified as embryonal carcinoma, 4 cases, teratoma, benign and malignant, 4, and choriocarcinoma, 2. A history of trauma was obtained in 5 cases.

The pathologic findings in each type are described and the dominating features are presented in photomicrographs. Vascular invasion was a poor prognostic sign.

Patients with seminoma were treated by orchiectomy and irradiation. Two patients died with widespread metastases within 1 year. At the end of 12 years, 3 were known to be alive. A number had been lost to follow-up.

Treatment of other germinal cell tumors was generally orchiectomy with para-aortic node dissection and irradiation in some. Prognosis was relatively poor, particularly in choriocarcinomas.

—*Allan K. Swersie, M.D.*

SURGERY OF THE GENITOURINARY TRACT

KIDNEYS AND URETERS

Duplicative Renoureteral Anomalies (I doppi distretti reno-ureterali). M. COLOMBATI, L. LUPATTELLI, and S. MESSINETTI. *Arch. ital. urol.*, 1960, 33: 273.

EIGHTEEN ANOMALIES of the renoureteral region are reported. These were all essentially what are generally designated "double kidneys" with bifid ureter or duplication of the ureter and were all observed and studied at the Institute of Clinical Surgery of the University of Perugia, Perugia, Italy from 1947 to 1959.

When the results of the authors are tabulated and compared with the data given in the world medical literature it is found that the incidence here given is lower, 15.5 per cent, than the figures generally furnished in the literature. Likewise, the authors' figures do not agree with those of the world literature with regard to the side affected, for in this material the right side furnished the greater incidence of these anomalies. In 4 of these patients both sides were involved. However, their figures do agree generally with the medical literature with reference to the age incidence, the majority of cases diagnosed being in the 40 to 60 year old patients, and in the matter of sex incidence, the greater number of cases being in the female sex.

Among the authors' patients the urinary disturbances which led to the recognition of the condition arose, in the majority of instances, as a result of the malformation itself—pyelitis and calculosis in 50 per cent of cases. There was only 1 case of tuberculosis.

In the matter of treatment, the authors point out that the majority of these patients benefited from medical measures. In 2 instances the pains were so severe as to require decapsulation of the affected kidney. There were 3 instances of heminephrectomy and 1 of nephrectomy. These operations were all necessitated by complications arising on the basis of the malformation itself.

The authors believe that the exereses were indicated in this material predominantly by the presence of complications and that the less extensive procedures are to be reserved for those patients in whom the manifestation consists solely of pain.

—*John W. Brennan, M.D.*

Diagnosis of Kidney Cancer. JOHN A. EVANS, MORDECAI HALPERN, and NATHANIEL FINBY. *J. Am. M. Ass.*, 1961, 175: 201.

EARLY DIAGNOSIS of cancer of the kidney will provide a good chance for cure. Of 100 consecutive histologically proved cases of renal cancer from the records of the New York Hospital, Cornell Medical Center in New York City, 84 per cent of the lesions occurred in patients between the ages of from 40 to 60 years, with a peak incidence between 50 and 60 years. The sex incidence showed almost a 2 to 1 male to female ratio.

The classic triad of symptoms—hematuria, pain, and mass—was seen in only about 10 to 15 per cent of these patients. Fifty-eight per cent of the patients in this series had gross hematuria. Only 1 patient had microscopic hematuria. Pain was uncommon and did not follow a constant pattern. Vague symptoms, such as fatigue or weakness, were occasionally noted. A mass was noted in 15 per cent of the patients. One-third of the patients in this series had no clinical indications of renal disease. Large renal neoplasms can be present without pain, hematuria, or recognizable mass. The illness usually consisted of intermittent episodes of nonspecific symptomatology.

Laboratory procedures, except for revealing hematuria and possibly polycythemia, were usually of no aid in diagnosis. The polycythemia appeared to be definitely related to renal cancer, since it disappeared after nephrectomy in 2 patients. Unexplained polycythemia may be a clue to renal cancer. The Papanicolaou test of the urine specimen was not helpful for hypernephroma. Studies were performed in 55 patients and all were negative for evidence of malignancy.

Hypernephromas were found equally in right and left kidneys and were evenly distributed between upper and lower poles. Calcification was present in 7 per cent. Almost all the hypernephromas were vascular neoplasms showing areas of necrosis and hemorrhage. Conventional and pyelographic studies permitted only a haphazard 50 per cent accuracy in differential diagnosis between renal cysts and tumors. Six patients had roentgenographic studies which revealed entirely normal findings. Fifty-eight patients showed either an enlarged kidney or a discrete mass related to the kidney. Calyceal abnormality was seen in 60 patients. Roentgenographic differentiation between renal cysts and neoplasm is not possible in most cases, except by the special technique of renal arteriography or nephrotomography. Nephrotomography has been the procedure of choice, showing an accuracy of 94 per cent in the differentiation of renal cyst and neoplasm.

—*Ray C. Johnston, M.D.*

The Presenting Manifestations of Obstructive Urinary Anomalies in Children. JOHN H. MCGOVERN. *Pediatrics*, 1961, 27: 3.

"BECAUSE the kidneys can be silently destroyed by obstruction alone, the great susceptibility of the obstructed tract to infection is in a sense fortunate, as the superimposed infection exposes the inadequacy of the urinary tract. Eradication of the obstruction is not always possible or may be attempted too late, but this is the fundamental mode of relief, the road to true therapeutic success." Having made this statement, the author goes on to describe in great detail case histories illustrating different presenting symptomatology. From a wealth of carefully studied cases, he has tabulated the presenting symptomatology of obstructive uropathy in children.

Fever was, of course, first in 31 per cent of the cases and pain was next, being the first symptom in 12 per cent of the cases. It is of interest to note that 12 of the 32 patients with pain as a presenting symptom under-

went operation before the true diagnosis was disclosed. Hematuria, dysuria, incontinence, and frequency, followed by gastrointestinal symptoms, obvious external abnormalities, and abdominal masses were also found.

The author comments that 47 per cent of these patients had had symptoms for 1 year or more prior to etiologic diagnosis being established. Forty-one per cent had recurrent infections. The author carefully points out that symptomatic therapy may temporarily alleviate the condition, but that urologic evaluation is imperative in children with persistent or recurrent infection.

Another interesting statistic is that 49 per cent of the patients were admitted to the hospital without a diagnosis of disease of the urinary tract.

The only way to prevent permanent renal damage is to diagnose and then alleviate the obstructive uropathy early in its course. This is the part of the alert pediatrician. —*John R. Herman, M.D.*

Urinary Tract Infections in Pregnancy. LAURI RAURAMO, ANTERO KASANEN, and KAARLO ELFVING. *Ann. chir. gyn. fenn.*, 1960, 49: 487.

A FOLLOW-UP EXAMINATION after 1 to 4 years established urinary tract infection in 21 or 23 per cent of 92 patients who had had urinary tract infection during pregnancy. In addition to the routine general examination, the follow-up included taking a sterile urine specimen, the phenolsulfonphthalein test, serum creatinine clearance, and a hemoglobin determination. One of the patients showed changes in renal function. Seven had slightly elevated blood pressure.

Urinary tract infection during pregnancy is not generally considered a serious disease. It is assumed that it clears up readily post partum once the predisposing factor has been eliminated. The symptoms of urinary tract infection are often so slight that the patient herself feels no concern about the disease. Infection is established, however, in every fourth subject as late as 1 to 4 years post partum. This is 2.5 times greater than the normal incidence of urinary tract infections in women. Obviously, urinary tract infection is a causative factor of chronic pyelonephritis. It is advisable always to pay adequate attention to the taking of a sterile urine specimen in postnatal examination from patients who have had urinary tract infection in connection with pregnancy or delivery. —*John R. Wolff, M.D.*

BLADDER AND URETHRA

Statistical Considerations on the Basis of 112 Cases of Vesical Papilloma (Considerazioni statistiche su 112 casi di papilloma vescicale). LUCIANO DELZOTTO. *Urologia*, Treviso, 1960, 27: 543.

AMONG THE ADMISSIONS to the Civil Hospital of Treviso, Italy in the 10 year period from 1949 to 1958 were 112, 1.98 per cent, patients with vesical papilloma, 3 of whom had diffuse papillomatosis. The treatment was by means of endoscopic fulguration, 243 sessions. The controlled hypotensive method of anesthesia, which results in less hemorrhage, has permitted more widely spaced endoscopic extirpations of a more radical character.

Sixteen of the removed specimens showed signs of malignant degeneration, the signs increasing in importance with each session on the same patient. In 36 instances the papillomatous lesion recurred and this group included 4 cases in which a partial cystectomy had been carried out. The highest incidence of recurrence was encountered among the very young—20 to 30 years of age—and the very old patients.

Associated diseases of the urinary tract occurred in 36 instances, the most frequent of these conditions being prostatic hypertrophy, particularly that of the middle lobe, 20 cases. Other concurrent morbid conditions were 15 cases of sclerosis of the neck of the bladder and 1 case each of bladder stone and of urethral stricture. This marked incidence of papillomatosis in cases of urinary stagnation is ascribed to the carcinogenic stimulus produced by the action of the beta-glucuronidase enzyme on the urine that is retained.

On the whole, complications were rare; there was 1 death, 0.89 per cent, of a patient with diffuse papillomatosis and 1 case of reintervention for the control of grave hemorrhage on the day after the fulguration.

In conclusion the author affirms that the treatment in all cases except those with urethral stenosis, evident malignant degeneration, and excessive size of the papilloma should be fulguration.

—*John W. Brennan, M.D.*

Surgical Therapy of Vesical Papillomatosis (Sulla terapia chirurgica della papillomatosi vesicale). D. FORTUNELLI, A. NAPOLITANO, and A. DI BARTOLOMEO. *Arch. ital. urol.*, 1960, 33: 298.

THE EXPERIMENTAL MATERIAL consisted of 10 dogs, of which 5 were subjected to removal by blunt dissection of the entire mucosal lining of the bladder, and 5 to an identical procedure with the exception of conservation of a cuff of mucosa around the ureteral apertures. Nine recovered without complication of any kind, urography and cystography at intervals after the intervention demonstrating no evidence of vesicoureteral reflux or of other abnormality in the functioning of the urinary apparatus.

In the animal which had died with symptoms of urinary sepsis, the vesical mucosa had reformed only partially, about the ureterovesical apertures. In all the other animals the mucosa had completely reformed. At the end of the first month this newly-formed mucosal covering of the denuded bladder wall consisted of a delicate membrane of a whitish or rosy color; at the end of the second and the third months this newly-formed mucosal covering had developed to the point of resembling in every respect the normal mucosal covering of the bladder walls. This was especially evident in the mucosal covering of the trigone, whereas in the fundus of the bladder the covering was still rather thin with only 2 or 3 strata of cubical or flat pavement cells. There was no noticeable difference in the healing process of those animals subjected to total and those subjected to partial removal of the bladder mucosa. In the other layers, such as the submucosa and the muscularis, there was revealed microscopically only a thickening of connective tissue in the submucosa.

The results obtained lead the authors to conclude that there is no contraindication to the application of this method for the clinical treatment of vesical papillomatosis. —*John W. Brennan, M.D.*

Dynamic Urethrography. GEORGE M. FISTER, RUSSELL L. NICHOLS, C. V. ZABRISKIE, and JOHN F. STUCKI. *J. Urol.*, Balt., 1960, 84: 733.

URETHROGRAPHY has proved to be an invaluable modality clinically and in research on the normal and abnormal aspects of micturition. The authors have developed a method suitable for general clinical use, utilizing double contrast visualization and aided by cineroentgenographic recordings.

Ideally, this modality includes detailed visualization of the entire urethra as well as the bladder base during retrograde filling and voiding. If possible, the ureterovesical juncture should be included during voiding in order to rule out reflux. The reason for using the double contrast is to prevent the opaque material from draping "umbrella-like" over the structure of the bladder floor. Carbon dioxide is utilized to fill the fundus of the bladder and to provide the "double contrast." The contrast medium used by these investigators is a barium suspension which is considered insoluble.

The authors describe in full detail the equipment and materials needed for their method. One most interesting and important idea is to insert a Foley catheter to the fossa navicularis and inflate it slightly in order to be able to hold it in the urethra.

This article is well worth studying by anyone to whom cineroentgenographic techniques are available. A new modification of one of the less well known techniques is presented in detail.

—*John R. Herman, M.D.*

The Onset of Stress Incontinence. WINIFRED J. A. FRANCIS. *J. Obst. Gyn. Brit. Empire*, 1960, 67: 899.

FOUR HUNDRED unselected women, 222 primigravidas and 178 multigravidas, attending a hospital antenatal clinic were questioned during and after pregnancy regarding stress incontinence. Cystometry was performed on all the 268 patients who complained of this symptom. Urethrocystography was carried out on a further 83 pregnant women, including 33 who suffered from stress incontinence and 50 with good bladder control.

Approximately 40 per cent of primigravidas give a history of having had occasional stress incontinence before pregnancy. Stress incontinence of urine rarely, if ever, appears for the first time after childbirth. It commences, if only in slight degree, either before or during pregnancy. The woman who has had stress incontinence before pregnancy is invariably worse during pregnancy. Incontinence present during pregnancy tends to disappear in the puerperium. It recurs, however, with each pregnancy and becomes progressively worse. Ultimately, and in certain women, it remains after delivery to become a persistent complaint.

The roentgenographic sign of "absent posterior urethrovesical angle" characterizes 90 per cent of the cases of stress incontinence seen during pregnancy, as it does in the nonpregnant state. The angle does not reappear immediately after delivery even though the patient recovers reasonably good bladder control.

It would seem that those women in whom stress incontinence develops in middle life are destined to do so from an early age but that pregnancy, rather than parturition, reveals the defect and makes it worse.

—*John R. Wolff, M.D.*

Correction of Urinary Stress Incontinence in Women by the Inguinovaginal Loop Operation (Operazione dell'ansa inguino-vaginale-retropubica per il trattamento della incontinenza urinaria relativa nella donna). VINCENZO FIACCAVENTO, GUY NARIK, and HANS-HADOLF PALMRICH. *Ann. ostet. gin.*, 1960, 82: 1179.

A SURGICAL PROCEDURE for the correction of urinary stress incontinence in women has been devised and routinely employed at the First Gynecological and Obstetrical Clinic of the University of Vienna Medical School, Vienna, Austria.

The operation is based upon the construction of a loop of aponeurotic material obtained from the external oblique fascia. The loop thus obtained is anchored around and in front of the urethra. To transfer the loop from the inguinal area to the preurethral position, a tunnel is obtained behind the pubic bone and in front of the bladder by means of blunt dissection. Care is taken to prevent damage to the important blood vessels of this region. The second stage of the operation is performed through a vaginal approach and the loop is sewed via an anterior colpotomy.

Fifty patients were operated upon with this technique and 30 of them were followed up for 6 to 8 months. The results were excellent in 27 cases, good in 2, and poor in 1. This operation, although developed primarily for the treatment of relapsing cases, can be used satisfactorily as a treatment of choice in all cases of urinary stress incontinence.

—*Maria Serratto, M.D.*

Urinary Continence and Normal Urination Provided by Urethral and Sphincter Substitution with a Special Seromuscular Segment of Ileum in Male and Female Dogs. KHALIL TORBEY. *J. Urol.*, Balt., 1960, 84: 717.

MEDICAL THERAPY, reconstructive surgery, and plastic surgical procedures have all been utilized in attempting to cure urinary incontinence.

The author has struck out in a new direction about this problem. The work was carried out, so far, only in dogs, but has shown considerable promise and should be followed closely.

Dogs are rendered incontinent by excision of the bladder neck, prostate, triangular ligament, and urethra in males, and the triangular ligament and urethra in females. These segments have been replaced by special seromuscular segments of ileum with excellent results from the standpoint of bladder function and urinary control.

Interestingly, the author found that maintaining the vascular arcade causes the segment to continue its tonus, peristaltic activity, and original length.

The author describes his operative techniques and his findings postoperatively. By the third week, the urothelium has usually covered the surface denuded of intestinal mucosa.

Dogs all established continence and good streams and none had any residuals after 1 week. Twelve month follow-up findings are offered. Urines gradually became clear and there were even some negative cultures made. In no case was the upper urinary tract disturbed. —*John R. Herman, M.D.*

ADRENAL GLANDS

Cushing's Syndrome. Louis J. Soffer, Angelo Iannaccone, and J. Lester Gabrilove. *Am. J. Med.*, 1961, 30: 129.

The authors present a study of Cushing's syndrome by analyzing a series of 50 patients, 43 females and 7 males, whose ages varied from 11 months to 68 years. Thirteen patients had adrenal carcinoma, 8 benign adrenal tumor, and 29 Cushing's syndrome associated with nontumorous adrenal cortical hyperfunction. The presence of an adrenal cortical tumor could be correctly established by perirenal or retrorectal gas insufflation in three-fourths of the tumor group. Clinically, some electrolyte abnormality was demonstrable in half of the patients; evidence of disturbance in carbohydrate metabolism was obtained in almost all. The urinary excretion of neutral 17-ketosteroids was increased in half the patients with nontumorous adrenal cortical hyperfunction, in one-third of the group with a benign adrenal tumor, and in two-thirds of those with adrenal carcinoma. All patients had an increase in the urinary excretion of either the formaldehydogenic fractions or the 17-hydroxycorticoids.

Treatment was determined by the nature of the adrenal disease. Adrenal tumors were removed surgically with proper preoperative preparation and postoperative care. In nontumorous adrenal cortical hyperfunction, pituitary radiation, unilateral adrenalectomy, or a combination of both measures was employed. In approximately 75 per cent of the entire group a satisfactory remission resulted. The remaining patients required a bilateral adrenalectomy. Postmortem studies were made of 13 patients and the findings are detailed in the article.

—*Gordon F. Madding, M.D.*

The Surgical Treatment of Cushing's Syndrome. Myron S. Roberts and John K. Lattimer. *J. Am. M. Ass.*, 1961, 175: 93.

The treatment of Cushing's syndrome has undergone a complete metamorphosis since the syndrome was first described by Harvey Cushing in 1932. Since the advent of cortisone and replacement therapy, subtotal or total adrenalectomy is now considered the treatment of choice by most surgeons.

The most important clinical findings in Cushing's syndrome are truncal obesity, hirsutism, hypertension, amenorrhea, decreased libido, plethora, striae, psychosis, weakness, backache, acne, headaches, and easy bruisability. In the series presented, 42 per cent of the patients had had their symptoms less than 1 year when first seen, the extremes being 2 months and 10 years. The more important laboratory findings included a diabetic glucose tolerance curve, elevated 17-hydrocorticoid and 17-ketosteroid levels, and osteoporosis. Aerogram studies are important in the preoperative evaluation of these patients. The accuracy of diagnosis was greater by means of the presacral pneumograms than with use of direct perirenal air insufflation. Statistical studies on 49 patients who underwent operation for the treatment of Cushing's syndrome at the Squire Urological Clinic, New York, New York are presented. The results showed that bilateral total adrenalectomy appeared superior to any other surgical method of treatment, including partial adrenalectomy for Cushing's syndrome due to adrenal hyperplasia. Subtotal adrenalectomy usually did not prevent the need for steroid replacement therapy and predisposed the patient to a possible additional operation if hyperplasia occurred in the remaining segment.

The preoperative preparation of a patient for contemplated adrenalectomy is most important. Cortisone is administered parenterally the day before and on the day of operation. An intravenous infusion of hydrocortisone is started as soon as the patient is totally adrenalectomized. Hypotensive anesthetic agents are avoided. The posterolateral incision is considered best for adrenal hyperplasias whereas the transperitoneal and thoracoabdominal approaches are preferred for suspected adenomas and carcinomas. There was a 12 per cent over-all operative mortality rate, with a 20 per cent over-all operative morbidity rate. Of the 49 patients who underwent surgical exploration for Cushing's syndrome, 10 per cent were found to have carcinoma, 17 per cent adenomas, and 73 per cent hyperplasias. Of the 11 patients who were subjected to bilateral total adrenalectomy none died postoperatively.

—*Ray C. Johnston, M.D.*

SURGERY OF THE MUSCULOSKELETAL SYSTEM

BONES AND JOINTS

Reduction of Anterior Dislocation of Shoulder Without Anaesthesia. DAVID K. EVANS. *Lancet*, Lond., 1960, 2: 1419.

KOCHER published his method of reducing anterior dislocation of the shoulder in 1870. Many new methods have been presented since then. A modification of Kocher's method easily performed without anesthesia is reported in this presentation. Reduction has been easily achieved by this procedure in 40 of 43 patients with such dislocations.

The patient lies face down on a couch with a pillow beneath the head and chest. The arm on the affected side is allowed to hang freely over the side of the couch, the dislocated shoulder projecting well over the edge of the couch. The surgeon sits on a low box and grasps the humeral epicondyles. His other hand is placed on the inside of the upper arm. The patient's forearm is flexed and lies across the bend of the surgeon's elbow. Slow steady traction is maintained, the arm being gently abducted, flexed forward, and slightly internally rotated. Reduction often occurs imperceptibly. In other cases, the hand in the axilla may be used to lift the head of the humerus into the glenoid cavity. —*Donald C. Geist, M.D.*

Roentgen Aspects of Injuries to the Pisiform Bone and Pisotriquetral Joint. ANTHONY VASILAS, VINCENT GRIECO, and NOEL F. BARTONE. *J. Bone Surg.*, 1960, 42-A: 1317.

FRACTURES of the pisiform bone and abnormalities of the pisotriquetrous joint space have received little consideration in the surgical literature. This communication reports the findings in 13 fractures of the pisiform bone and other abnormalities in this area.

There are no well-defined criteria for the roentgenographic diagnosis of subluxation of this joint. Study of this group of injuries suggests that certain roentgenographic views must be used. These are (1) dorsipalmar with the wrist in the neutral position; (2) dorsipalmar with ulnar deviation of the wrist and slight elevation of the ulna produced by 10 degrees of further pronation of the forearm; (3) palmar-dorsal with the forearm in the supine position, that is, to 30 degrees of supination from the straight lateral position, the ulnar side down and the thumb up and out; and (4) the tunnel view.

Fractures of the pisiform bone were found in 13 cases collected from 6,000 roentgenographic examinations of the wrist. Seven were isolated fractures and the remainder were associated with other fractures in this region. There were 7 linear and 6 comminuted fractures. Marked displacement of the fractured fragments occurred in only 1 patient. The articular surface of the bone was involved in 11 of 12 cases. Direct trauma seemed to be the common mechanism. Treatment consisted in immobilization in a splint or cast for 3 to 6 weeks. Union was usually complete in 4 to 6 weeks. The patients regained normal function.

A roentgenographic study of the kinematics of the triquetrous space was undertaken to determine the changes in the joint occurring in this fracture. The normal triquetrous joint showed marked deviation of the joint space as to parallelism, width, and alignment of the articular surfaces in all roentgenographic positions used but the neutral position. Only this position, therefore, can be used to evaluate the pisotriquetrous joint space after injury. The roentgenograms were adequate in 40 fractures of the lower end of the radius for this evaluation. In 28 of these, the joint space was normal. In 12 cases there was alteration of the joint space. Eleven patients had an increase in the width of the space and 6 had lost the normal parallelism. Five revealed overriding of the surfaces. There was no correlation between the abnormality of the joint space and the severity of the fracture of the radius. Abnormality of the joint occurred in only 1 of the fractures of the pisiform bone. Treatment of the fracture in most cases returned the triquetrous joint to normal.

It would appear that subluxation of the triquetrous space is of clinical significance when associated with fractures of the distal portion of the radius.

—*Donald C. Geist, M.D.*

Surgical Treatment of Rheumatoid Hand. EDWARD D. HENDERSON and PAUL R. LIPSCOMB. *J. Am. M. Ass.*, 1961, 175: 431.

THE TECHNIQUES used by surgeons in the reconstruction of hands after trauma are found to be useful in certain patients whose hands have been affected by rheumatoid arthritis. The patient must be carefully selected with regard to motivation and ability to cooperate in the postoperative program. Emphasis is placed on restoration of function rather than on cosmetic appearance and on early, simple procedures rather than late, complicated operations. Operations are described for the correction of wrist flexion deformity, tenosynovitis, tendon rupture, intrinsic muscular contracture, ulnar drift of the finger, dislocation of proximal joints, instability of the thumb, and deformity of finger joints. The operations are designed to supplement rather than to replace conservative measures of treatment of rheumatoid arthritis of the hand.

Roentgenologic and Histologic Investigation of Postoperative Loss of the Correction Obtained by Spinal Fusion in Scoliosis (Roentgenologische und histologische Untersuchungen zur Frage des postoperativen Korrekturverlustes bei skoliotischen Wirbelsaeulenversteifungsoperationen). H. A. HIENZ and H. MAU. *Zschr. Orthop.*, 1960, 93: 477.

IT APPEARS that a modified Hibbs technique, in cases in which laminae, spinous processes, and articular facets form a solid mass of bone, is more prone to maintain correction than is the Albee type of spinal fusion. The loss of correction occurs in the immediate postoperative period in which the correction is

maintained by external fixation by either cast or brace. The correction may also be lost at a later stage after all immobilization has been discontinued. Loss of correction may be the result of poor judgment in deciding how many vertebrae are to be fused or lack of correction of a pelvic obliquity.

A large number of failures are found in cases in which a pseudarthrosis develops or may be caused by the formation of an area of "immature bone."

Spines of 8 patients of a series of 50 had to be reoperated on because of the formation of pseudarthrosis. In most cases after exposure of the weakened section of the fusion, a 3 to 4 cm. long area was found within, showing a smooth, glistening surface forming small protrusions within the pseudarthrosis. Usually a transverse defect in the bone mass was seen measuring about 1 to 2 mm., filled with fibrous tissue. The histologic examination of these areas showed islands of hyaline cartilage and fibrous cartilage.

Reproductions of roentgenograms and histologic sections were included to demonstrate these changes. The clinical significance of the areas of "immature bone" is still in doubt. It may be the first stage of future formation of a pseudarthrosis, it may be caused by a lack of proper immobilization during the immediate postoperative period, or it may be the result of improper operative technique in which, in this particular area, improperly prepared bone chips surrounded by fibrous tissue were placed and which later on formed the defect.

An analysis of the failures of spinal fusion for correction of scoliosis revealed the presence of any one of the following factors: (1) bad general condition of the patient, caused by severe scoliosis; (2) infection in the operative field; (3) lack of correction of the pelvic obliquity prior to the operation, particularly in cases of paralysis; (4) residuals of a severe kyphosis and extreme correction of the spine; (5) insufficient fusion of the vertebral bodies; (6) unsatisfactory postoperative fixation; (7) premature weight bearing; (8) insufficient amount of bone mass to sustain bony fusion; and (9) faulty technique particularly in the preparation of the bone fragments.

The author concludes that postoperative fixation of the spine after spinal fusion to correct scoliosis should be maintained for at least 1 year.

—George I. Reiss, M.D.

Diagnostic Significance of Asymmetry of the Thigh Folds and the Gluteal Folds (Die Asymmetrie der Oberschenkel- und Gesaessfalten und ihre diagnostische Bedeutung). W. H. E. Schneider. *Zschr. Orthop.*, 1960, 93: 508.

The author examined 100 children between the ages of 0 and 3 years in 1957 and discovered that 71 showed asymmetry of the thigh folds. The roentgenographic examination of these children revealed that 47 had no pathologic condition in the joint, 22 had subluxation and mild dysplasia of the acetabulum, and 2 had unilateral dislocations of the hip. Dissimilarity of the femoral neck angles was discovered in 56 children with asymmetry of the thigh folds, whereas in 2 children who showed asymmetry of the thigh folds, no difference in the femoral neck angles could be observed. It is significant that also in children who had symmetrical thigh folds, the majority showed a difference in the femoral neck angles.

Asymmetry of the gluteal fold is caused by the changes in the position of the greater trochanter; therefore, coxa vara, faulty torsion of the neck and shaft, and internal rotation of the femur have a tendency to accentuate the gluteal folds, whereas external rotation of the hip has a tendency to flatten them. A follow-up examination of 20 children who have had asymmetry of the thigh folds and gluteal folds but normal hip joints was made. All of them at birth had asymmetrical thigh folds and gluteal folds but showed no disorder of the hip joint and when re-examined at the end of 10 years also had normal appearance of the hip joints. In 6 of these children a shortening of the leg was observed, in most of them less than 2 cm. In 14 children a mild scoliosis was found.

—George I. Reiss, M.D.

Hip Prosthesis Locked in the Acetabulum and the Shaft. P. M. Girard. *Texas J. M.*, 1961, 57: 7.

The author describes the use of a dual lock, curved stem type prosthesis. This prosthesis has been very useful in cases in which difficult nursing care was to be anticipated and was particularly efficacious and practical in mental patients whose co-operation was not possible. No special instruments are required for its insertion. Because of the locking features, the same size stem fits in any case. The author has used only the medium-sized head in all of the cases, simplifying the purchasing problem of the hospital. By using this type of prosthesis which allows early ambulation, the hospital stay of patients is reduced considerably. The first prosthesis was inserted in 1953. The latest models, used in the past 2 years, show deflection only after more than 950 pounds of pressure have been applied. None has broken. A number of cables have frayed and broken in the head area after approximately 1 year's use. This is of no significance, however, as after that time the cable's usefulness has ended. The author knows 9 different surgeons and a number of resident surgeons who have used this type of prosthesis in 166 cases.

The author uses an L-shaped incision on the lateral side of the trochanter and upper shaft, tailing the upper end toward the iliac crest to a point approximately 7 cm. behind the anterosuperior spine and 3 cm. below the iliac crest. Capsule structures which can be reached should be removed since calcification and scar in the capsule will cause pain and stiffness. The femoral head is removed. The author prefers to extract the head using lion jawed femur holding forceps. The round ligament remnant is removed from the acetabulum.

With the patient's leg in 90 degree external rotation, the cross knee position, the operator drills three holes five-sixteenths of an inch in diameter parallel and near each other through the proximal cortex but at right angles to the shaft. Location of these holes is determined by using the prosthesis as a guide against the neck and shaft after proper washers have been selected. A hole five-sixteenths of an inch in diameter is drilled through the acetabulum in the superior center portion just inferior to the joint cartilage. The hole should be at the site of the superior attachment of the

round ligament. A curved forceps, preferably a tonsil or common bile duct right angle forceps, is passed around the hole inside the pelvis to loosen adjacent muscle attachment. The T bar is inserted in horizontal position; the vertical position is avoided because of the obturator nerve. To insure that the bar is locked inside the pelvis, the cable is pulled. A wire is attached to the end of the cable and the wire is clamped to drapes out of the way.

Because of the locking of the head of the prosthesis into the acetabulum and of the stem into the shaft of the femur, dislocation is not possible and, therefore, no cast or splint is necessary in the immediate postoperative care, nor are special nursing instructions such as "avoid adduction or external rotation" required. —*C. Fred Goeringer, M.D.*

The Varus-Producing Osteotomy of Pauwels (A propos de l'ostéotomie de varisation de Pauwels). J.-J. HERBERT. *Mém. Acad. chir.*, Par., 1960, 86: 810.

THE AIM of Pauwels' operation is a transtrochanteric cuneiform resection osteotomy which is based medially. This of course reduces the cervicodiaphysial angle by 20 to 30 degrees and therefore corrects a valgus into a varus position of the femoral neck. As a result, the weight-bearing surface of the femoral head is increased. The author describes with the help of diagrams how Pauwels' operation produces an elevation of the femoral shaft and therefore a significant shortening. A modification of Pauwels' operation is described with the aim of decreasing this shortening. The angle of the cuneiform resection is reduced by half. A simple osteotomy is then made externally at the level of the greater trochanter and the wedge which has been resected medially is rotated 180 degrees and is impacted into the osteotomy. This achieves the same degree of varus as Pauwels' operation but less shortening.

The author describes his own preferred technique which he claims produces still less shortening. A simple incomplete intertrochanteric osteotomy is performed. It does not include the medial cortex. The required angulation is then performed without disrupting the continuity of the medial femoral cortex. This position is maintained by means of an intramedullary rod, and the osteotomy space is filled in with a sliding bone graft and bone chips. In case of associated adductor spasm, adductor tenotomy and/or osteotomy of the lesser trochanter is performed. A long hip spica is applied for 3 weeks followed by a short spica for another 5 to 6 weeks. During the latter period the patient is ambulated on crutches. No weight-bearing is allowed until full consolidation occurs about 2 months postoperatively.

The author has applied this technique in 6 cases and claims excellent results with no or minimal shortening. The correction of the cervicodiaphysial angle has varied from 20 to 30 degrees.

—*Joseph J. Bahuth, M.D.*

Arthrodesis of the Ankle with Particular Reference to the Gallie Procedure. J. C. KENNEDY. *J. Bone Surg.*, 1960, 42-A: 1308.

THE AUTHOR has gathered 50 cases of ankle arthrodesis for clinical analysis. Of particular interest to him is the Gallie procedure for ankle fusion frequently confused with the Gallie posterior approach for subtalor fusion. The author performed 20 fusions and 3 other surgeons performed the others, each adhering to a single technique. The other methods were the so-called Watson-Jones anterior, the Charnley compression, and the Crawford-Adams lateral transfibular fusions.

The indications for operation were as follows: Trauma, 29; poliomyelitis, 9; tuberculosis, 4; osteoarthritis, 5; and miscellaneous, 3.

Gallie approached the ankle both medially and laterally through separate incisions. He did not debride the cartilage and he used homogenous bone. The author has modified the procedure; he debrides the cartilage, uses staples for internal fixation, and uses heterogenous bone. Of 20 patients, 17 had "very satisfactory results with a minimum of constant complaints." Two had indifferent results, and 1 had a poor result. The Gallie procedure is especially indicated in those patients whose epiphyses are still open.

The most important point the author makes is that the poorest results are obtained in those patients who have pre-existing pathologic conditions in other joints of the foot. Postfusion pain is a puzzling entity. It occurs in one-third of the patients and usually is located just anterior to the lateral malleolus.

—*Richard G. Saxon, M.D.*

MUSCLES AND TENDONS

Tumors of the Tendon Sheaths (Geschwuelste des Sehnengleitgewebes). H. MITTELMEIER. *Zschr. Orthop.*, 1960, 93: 385.

IT IS NOT always possible to decide whether a tumor arises from the tendon or the tendon sheath, but it seems that the majority of the tumors under discussion arise from the sheath. The sheath is of mesenchymal origin and only mesenchymal tumors are to be expected. The reactive powers of active mesenchymal tissue are great and many pseudotumoral formations must be differentiated from the true tumors. The author discusses three groups of tumors: benign, malignant, and false tumors.

Although fibromas are often described, the growths are in reality giant cell tumors. Just as in the tendons, fibromas are extremely rare in the tendon sheaths. Benign giant cell tumors or fibroblastomas are typical tumors of the tendon sheaths. About 100 cases have been described in the literature. Usually they attain the size of a bean and their common location is in fingers or toes. They have an irregular surface macroscopically, but are nevertheless well defined tumors. They are not as firm as true fibromas. The sectioned surface is white with yellow areas. Histologically, one finds mesenchymal cells and many giant cells. The cells have no malignant characteristics. Xanthoma cells and brown iron pigments are frequently seen.

Knuckle pads occur at the dorsum of the middle interphalangeal joints and are not to be considered true fibromas. They are found only on the middle joints, are multiple, and appear on all fingers except the thumb. They grow to the size of a bean and then

remain constant. The author finds these knuckle pads to be fixed firmly to the extensor mechanism of the fingers. They consist of cellular mesenchymal tissue, morphologically resembling the mesenchymal tissue in Dupuytrens' contracture.

Lipomas usually occur in the extrafascial subcutaneous tissues. In rare instances, however, lipomas have been described in the subfascial tissues of the palm. Chondromas and myxochondromas of the tendon sheaths are very rare. The author describes a case of a chondroma between the extensor tendons and the periosteum of the third and fourth finger with bony atrophy. An osteochondroma under the Achilles tendon in the gliding layers of the deep muscles is described.

Only 1 case of a hemangioma of the tendon has been described but reports of many hemangiomas arising from the paratenon were found in the literature. Lymphangioma is mentioned. The so-called lipoma arborescens presents a mixed histologic picture. Tumors consisting of telangiectatic vessels, fibrous tissue, and muscles and located in the finger tendons are described. Recently, malignant and benign synoviomas have been compared. Fibroblastomas, endotheliomas, fibromas, and xanthomas have been included, however. No definite decision has been made as to whether Jaffe's pigmented villonodular synovitis is a tumor.

Malignant tumors arising from tendons and tendon sheaths are extremely rare. Most of the cases reported in the older literature were probably benign giant cell tumors. Malignant synoviomas are characterized by slow growth. Sometimes years pass before lung metastases occur. The histologic picture is also variable and the interpretation of the biopsy difficult.

Wrist ganglia and xanthelasma are pseudotumors, not true tumors. —*J. C. Mulier, M.D.*

Anterior Transplantation of the Posterior Tibial Tendon for Persistent Palsy of the Common Peroneal Nerve. PAUL R. LIPSCOMB and JAMES J. SANCHEZ. *J. Bone Surg.*, 1961, 43-A: 60.

THE PERTINENT ENGLISH LITERATURE pertaining to anterior transfer of the posterior tibial tendon is reviewed, and the case histories of 10 patients treated in this manner at the Mayo Clinic are analyzed. All had posterior tibial tendon transfers in a long spiral manner around the medial surface of the tibia to the dorsum of the foot, together with triple arthrodesis, for persistent palsy of the common peroneal nerve.

The results of this study indicate that transfer of the posterior tibial tendon to the dorsum of the foot satisfactorily restores the ability to dorsiflex the foot when persistent palsy of the common peroneal nerve is present. A transfer of the posterior tibial tendon around the tibia rather than through the interosseous membrane functions satisfactorily if the original technique described by Ober is adhered to. Transfer of the posterior tibial tendon should be accompanied by stabilization of the foot, except perhaps in the young child.

Because of the comparative frequency of persistent palsy of the common peroneal nerve, there must be a large number of persons who have an annoying equinovarus gait or who wear a brace because of this deformity. It is suggested that such persons could be greatly benefited by anterior transplantation of the posterior tibial tendon.

SURGERY OF THE VASCULAR SYSTEM

BLOOD VESSELS

Hydrogen-Platinum Electrode System in Detection of Intravascular Shunts. ALBERT L. HYMAN, EDWARD S. HYMAN, ANTONIO C. QUIROZ, and JAMES R. GANTT. *Am. Heart J.*, 1961, 61: 53.

RECENT ADVANCES in cardiovascular surgery emphasize the need for more accurate techniques in preoperative diagnosis of cardiac abnormalities. With a modified Clark hydrogen-platinum electrode system, hydrogen labeled blood is detected as it reaches the right side of the heart because of the change in oxidation potential as registered by the platinum electrode at that site. Studies in 34 patients in whom intravascular shunts were suspected were made. The comparative sensitivity of the hydrogen platinum electrode, dye dilution, and oxygen methods were also evaluated in 5 dogs with subclavian-pulmonary artery anastomoses. This modification has proved to be a reliable, simple, and accurate method for the detection and localization of small left to right shunts. Details of the system and its equipment are provided. The technique can be repeated as frequently as necessary at the catheterization table without the withdrawal of samples of blood for dye curves or the insertion of multiple catheters. The extreme sensitivity of the method, however, serves as a disadvantage in the presence of large shunts when valvular regurgitation is likely to occur. —*Allan D. Callow, M.D.*

New Findings in the Coronary-Encephalic Perfusion in Depressed Surgical Cases. ALFONSON TOPETE, HECTOR HUIZAR LARA, J. TRINIDAD PULIDO, and GUILLERMO DIAZ CARO. *J. Thorac. Cardiovasc. Surg.*, 1960, 40: 161

ACUTE BLOOD LOSS of 90 to 95 per cent was obtained by intra-arterial bleeding and suction in 275 dogs. Blood replacement was made by coronary-encephalic perfusion whereas control dogs subjected to similar blood loss were reinfused either intravenously or intra-arterially. The survival rate was 3.03 per cent of 132 dogs transfused intravenously after blood drainage. Intra-arterial transfusion yielded a survival rate of 5.08 per cent in 118 dogs. Immediate therapeutic coronary perfusion in 200 dogs yielded a survival rate of 90 per cent. Perfusion within 2 minutes after hemorrhage resulted in a 79 per cent survival rate whereas therapy applied after a waiting period of 4 to 6 minutes changed the mortality rate to 89.07 per cent. In all of the latter experiments, the blood was pumped through a plastic tube which had been introduced into the femoral artery and advanced to the superior third of the descending thoracic aorta. In a smaller group of 25 dogs the same results were obtained when blood was returned by way of the abdominal aorta.

A total of 50 patients were treated by the perfusion technique described. Of a group of 28 patients in severe hemorrhagic shock due either to accidental trauma or major surgery the response to this treatment was satisfactory except for 2 failures. The most radical types of operation were tolerated by 22 severely debilitated and hypotensive patients under perfusion. —*Benjamin G. P. Shafiroff, M.D.*

A Report of 15 Patients with Traumatic Rupture of the Thoracic Aorta. F. C. SPENCER, P. F. GUERIN, H. A. BLAKE, and H. T. BAHNSON. *J. Thorac. Cardiovasc. Surg.*, 1961, 41: 1.

APPROXIMATELY 10 to 20 per cent of patients suffering traumatic rupture of the thoracic aorta survive. Usually they fall into 1 of 2 groups: those in whom the hemorrhage is contained in a hematoma but who may die of delayed rupture within the first few weeks after injury, and those surviving the initial and delayed threat but in whom a false aneurysm develops which may remain stable for months or years. Fifteen patients are reported, 7 seen soon after aortic rupture and 8 seen with an aneurysm months or years after injury.

It is remarkable that aortic transection may be present with remarkably few external signs of injury and that there is often time for the institution of reparative treatment. The most helpful diagnostic aids are a wide mediastinum on the chest roentgenogram and a history of injury.

The most common cause of aortic laceration is the automobile accident. Uncommon causes include fall from a height, direct crushing blows to the chest, or a sudden rise in intravascular pressure such as that caused by being covered with earth in a mine cave-in. The difference in rate of deceleration of the mobile descending thoracic aorta and the relatively fixed arch of the aorta strains the junction of these two areas at the aortic isthmus where the ligamentum arteriosum is attached. The commonest site of aortic injury is usually just distal to the left subclavian artery and the next most common site is the ascending aorta. The aortic tear is a transverse one which may extend through the intima and media with preservation of the adventitia or through all layers with retraction of the two ends. Patients who do not exsanguinate immediately are probably those in whom the adventitia remains intact for a short time. Delayed death from hemorrhage rarely occurs after 4 weeks, contrasting markedly with death from aneurysms of syphilitic or arteriosclerotic origin.

Awareness of the fact that aortic rupture can occur with any chest injury is the first step in diagnosis. Any degree of widening of the mediastinum on the chest roentgenogram should be carefully investigated, and progressive widening without symptoms probably is an adequate indication for immediate thoracotomy. Preferred treatment is excision and replacement with a plastic prosthesis preferably of woven teflon. The distal circulation is supported with left atrial-femoral artery bypass.

Results have been good, mortality low. Small asymptomatic aneurysms may be faithfully observed if there is additional disease present which makes operation hazardous. A tabular review of 43 cases is included. —*Allan D. Callow, M.D.*

Surgical Management of Penetrating Injuries of the Ascending Aorta and Aortic Arch. WALTER L. DIVELEY, ROLLIN A. DANIEL, JR., and H. WILLIAM SCOTT, JR. *J. Thorac. Cardiovasc. Surg.*, 1961, 41:23.

THREE PATIENTS, 1 who received a bullet wound which injured the aorta and pulmonary artery, a second suffering penetration by a heavy, rusty wire thrown by a power lawn mower with injury to the same vessels and extension into the trachea, and the third who sustained a knife wound which perforated both walls of the aorta and the wall of the right atrium as well, are described. Each was operated on with successful repair and recovery.

In 2 patients a fistula was established between the aorta and pulmonary arteries, two vessels in which there is normally a high pressure differential. Both of these wounds were located within the pericardial sac, and it is speculated that cardiac tamponade occurred and may have been lifesaving, in that the flow of blood from the aorta may have been slowed to the extent that thrombus formation in the aortic wound prevented further hemorrhage. In the patient with injury to the wall of the right atrium extracorporeal circulation was necessary for repair but was not utilized in the 2 other patients. Details of clinical findings, roentgenograms, and operative steps are included. —*Allan D. Callow, M.D.*

Aortic and High Pelvic Arterial Occlusions (Das Schicksal von 226 Patienten mit Aorten- und hochsitzenden arteriellen Beckenverschluessen). JOHANNES PAUL SCHRÖDER. *Med. Welt.*, 1960, p. 2588.

THIS REPORT from the Surgical Division of the City Hospital of Leverkusen, Germany deals with the fate of 226 patients with verified occlusions of the abdominal aorta and the hypogastric arteries. A 10 year period is covered.

There was present in almost all the patients obliterative vascular disease in the peripheral and coronary arteries as well. Among the 36 with complete aortic occlusion nearly one-third died on an average of 7 years after onset of symptoms. One-fourth of the patients with extensive pelvic arterial occlusions died during this 10 year period. For both groups, left heart failure and myocardial infarction were the most frequent causes of death.

Therapeutically only sympathectomies and a few thrombendarterectomies were performed. Encouraged by the good results reported from the literature the author's clinic has changed over to more aggressive surgical intervention. —*Hans J. Schweizer, M.D.*

Studies on Patients with Arteriosclerotic Obliterative Disease of the Femoral Artery. R. WARREN, H. T. JOHN, R. C. SHEPHERD, and J. L. VILLAVICENCIO. *Surgery*, 1961, 49: 1.

THE AUTHORS REPORT their results with femoral artery reconstructions for arteriosclerotic obliterative disease. They point out the difficulty of drawing valid conclusions because most reported work has been limited by the difficulty of procuring pertinent information concerning selection of patients, indications for operations, lack of histologic material from human beings, and the problems of interpretation of preoperative and postoperative arteriograms. Postoperative arteriograms revealed abnormalities including aneurysm, localized constriction, generalized constriction, dilatation, and absence of any demonstrable lesion in 77 per cent of 54 limbs studied. Thromboendarterectomized segments which closed later than 1 year postoperatively caused no deterioration of the circulation beyond its preoperative status presumably because of concomitant collateral vessel formation, with the result that many late closures after thromboendarterectomy have been entirely asymptomatic. After bypass procedures, on the contrary, the worsening of limb condition after late closure is little different from that which follows early closure.

The authors make a plea for a standardized method of reporting results and urge that a major effort continue for the development of an ideal prosthesis. They advise reconstructive operation for all patients with an adequate artery distal to the block who have rest pain or gangrene. Only patients who suffer from intermittent claudication are advised to postpone operation until the day when symptoms may become worse.

For those patients who present severe claudication as well as coldness, numbness, and poorly defined discomforts in the leg and thus represent an intermediate group, about half in the authors series, the decision must be an individual one. The authors note the narrow margin between a brilliant success with complete relief on one hand and failure with worsening of the circulation and possible amputation on the other. —*Allan D. Callow, M.D.*

Spontaneous Portacaval Anastomoses (Les anastomoses porto-caves spontanées). PHILIPPE DÉTRIE and ROALD MARTINI. *J. chir.*, Par., 1960, 80: 452.

SIX CASES of spontaneous portacaval anastomoses are presented. The patients' ages ranged from 3 to 49 years. The presenting picture was one of hematemesis in 3 cases with or without painful abdominal crises and hepatosplenomegaly. There was a past history of abdominal thrombosis in 3 cases. In the 3 year old patient the most likely cause was a congenital anomaly or absence of the portal vein.

The diagnosis was confirmed by splenoportography which usually results in nonvisualization of the portal vein beyond the vertebral column and visualization of important portacaval anastomotic vessels. Splenomanometry showed elevated pressures, above 250 mm. of water in 4 of the 6 patients. Other roentgenologic examinations included cavography and ileoportography. The liver function tests were impaired.

Operation was performed on 5 patients: splenectomy in 3, portacaval shunt in 1, and alcoholization of the splanchnics in the other. A detailed anatomic study of the portacaval anastomoses is given, corroborated by postmortem examination of 100 specimen and studies of 18 fetuses. Five classical groups of anastomotic vessels are described: (1) the gastroesophageal; (2) those of the distal portion of the large bowel; (3) those of the round ligament; (4) the retroperitoneal; and (5) miscellaneous veins. However, the authors emphasize the importance of a sixth one recently described by Gillot and Hureau—the gastrophrenocapsulorenal venous trunk. This originates from the submucosa of the upper half of the stomach,

is oriented at first from right to left toward the gastroesophageal junction, then changes direction, being oriented inferiorly and posteriorly, and, through the vein of the left diaphragmatic pillar, ends in the midcapsular and left renal veins and thence, finally, in the inferior vena cava. This venous trunk was found to be present in 16 of 100 dissections performed by the authors and in 11 per cent of the fetuses. It was also the main anastomotic trunk in certainly 3 and probably 2 more of the 6 patients presented. Other important anastomoses are the perigastroesophageal, responsible for the hematemesis.

Despite these different ways of shunt the portal pressure remains invariably high. Possible causes for this are examined. The anastomotic vessels represent no potential danger and are naturally pre-established shunts, so the authors conclude that they should be respected at operation.

—Giuliano Di Bartolo, M.D.

Thrombolysis with Infusions of Purified Streptokinase (Thrombolyse durch Infusionen hochgereinigter Streptokinase). RUDOLF GROSS, WALTER HARTL, GERHARD KLOSS, and BURKHARD RAHN. *Deut. med. Wschr.*, 1960, 85: 2129.

UPON intravenous infusion of streptokinase almost all of the plasminogen in the blood is transformed into the active protease plasmin. Because of active proteolysis a decrease in fibrinogen may occur during this period. Unusually active fibrinolysis may be inhibited by certain amino acids; ϵ-aminocaproic acid is a useful antidote.

The indications for fibrinolytic therapy by itself or in conjunction with other procedures are most thrombotic or embolic processes of reasonably recent development. In the authors' experience, treatment with thrombolytic agents carried less risk than anticoagulation. Bleeding tendency and a history of streptococcal-allergic diseases were considered to be a contraindication to streptokinase therapy.

The authors administered a total of up to 885,000 U. of streptokinase to 13 patients; the initial dose was 40,000 to 100,000 U. A combination of streptokinase with adrenal steroids and in selected patients with anticoagulants was found useful.

Complications such as temperature elevation necessitated discontinuation of therapy in 10 per cent of the patients. Even though in most patients with thrombophlebitides, cerebral and pulmonary emboli improvement after therapy was measured by rather subjective criteria, lysing of arterial occlusive thrombi was documented by well executed arteriograms.

—Karel B. Absolon, M.D.

Left Common Iliac Arterial Embolectomy in the Newborn. WILLIAM HENRY, BENJAMIN B. JOHNSON, and ARNOLD L. PETERSEN. *West. J. Surg.*, 1960, 68: 352.

EMBOLISM of a major artery in a newborn infant is a relatively rare occurrence. The authors review literature in which reference is made to cases of gangrene of the arms or legs in the newborn and autopsy evidence that the embolus may originate from thrombosis of the ductus arteriosus. Another origin of the clot may be that a thrombus occurring during the transformation of the patent umbilical artery to its thrombosed state may extend in a retrograde direction into the iliac artery.

The authors report 2 cases of thrombosis of the left common iliac artery. Embolectomy was performed in both cases. One case ended fatally and at autopsy a thrombus was found in the left auricular appendage, with a soft red thrombus in the ductus arteriosus. The second patient made an uneventful recovery.

These are possibly the first surgically treated patients whose cases are reported.

—Carl H. Calman, M.D.

Thromboembolism in Cardiac Surgery. LAURENCE MISCALL, RICHARD B. NOLAN, and HARRIS ANDERSON. *West. J. Surg.*, 1960, 68: 354.

THE AUTHORS discuss the formidable problem of peripheral arterial embolism as a complication of operation on the mitral valve. In some series the incidence of atrial thrombosis and arterial embolism is very high.

The authors attempt to evaluate the value of anticoagulation in avoiding this complication. Two groups of 35 patients each are compared. The control group received no anticoagulant treatment. The test group received dicumarol before operation for at least 3 weeks, prothrombin time being maintained at 2 to 2.5 times normal. Anticoagulation was continued during the operative and postoperative period for 3 weeks or longer.

The anticoagulated patients had no postoperative thromboembolic complications; there were 9 complications in the untreated group. There were 6 cases of mild, and 5 of severe postoperative bleeding in the anticoagulated patients, some losing 7 liters of blood in the first 24 hours. *—Carl H. Calman, M.D.*

Thromboembolic Disease at the University Women's Clinic in Leipzig from 1937 to 1956 (Die thromboembolischen Erkrankungen an der Universitacts-Frauenklinik Leipzig der Jahre 1937–1956). REINHOLD SCHWARZ and REINHARD TROMMER. *Gynaecologia*, Basel, 1960, 150: 229.

THERE WERE over 68,000 admissions to the Gynecologic Service of the Woman's Clinic of Leipzig, Germany during a period of 20 years with 174 instances of thrombophlebitis and 57 of pulmonary embolism. The incidence for thrombosis varied from 0.67 per cent after serious operations to 0.04 per cent in conservatively treated patients, with an average of 0.26 per cent. After the war, with its peak incidence of thromboembolic disease, pulmonary embolism rapidly decreased and started to rise again in the past few years. It appears that operation for prolapse and abdominal hysterectomy for fundal cancer had the highest morbidity, but this would not influence indications and procedures materially. It was interesting to observe that extrauterine pregnancies carried a relatively high incidence of thrombosis; that the thrombi were unusually large and occurred long after radical operation; and that radium treatment is no better than laparotomy in this respect.

In a group of nearly 70,000 deliveries during the same period 852 instances of thrombophlebitis, 1.2 per cent, and 56 of pulmonary embolism were seen. Of these, only 12 embolisms were fatal in contradistinc-

tion to postoperative embolism with about two-thirds mortality figures. Operative deliveries in 8,000 cases, including outlet forceps, doubled the morbidity from this cause, and morbidity reached 12.9 per cent in high forceps applications. Nearly one-half of these complications occurred during the first 3 postpartum days. —*W. Dieter Bergman, M.D.*

Fibrinolysin Therapy. HIROSHI OUCHI, JOHN S. BELKO, and RICHARD WARREN. *Arch. Surg.*, 1961, 82: 88.

THE AUTHORS report their experiences with lysis of experimental blood clots with human plasmin or fibrinolysin prepared from fraction III of plasma and activated with streptokinase. The authors' modified method for assay of fibrinolytic activity is described.

Standard intravascular clots were created in dogs by crossclamping the jugular vein and coagulation was initiated by aspirating, then reinfusing the stagnated blood. Varying amounts of plasmin, averaging 45,000 units, were mixed in 100 ml. of saline and injected into the forelimb vein at a rate of 100 ml. per hour over periods varying from 2 to 12 hours. If concentration of fibrinolysin was maintained at 900 to 1,350 units/ml., the clots were usually dissolved within 1 hour when infusion was started 2 cm. proximal to the main branches. Such local infusion was effective on clots up to 5 days old. The time factor is important, and total lysis may be procured with lower concentrations and smaller total amounts of fibrinolysin when infusion is extended from 1 to 2 hours.

Systemic infusion requires approximately 4,000 units per kilogram of body weight to maintain fibrinolytic activity in the blood. Observation of the effects of systemic infusion in humans reveals that the amounts required to induce a fibrinolytic state vary a great deal more in humans than in dogs. The smallest dose that caused effective fibrinolytic activity was 1,200 units/kgm./hr., with an adequate dose estimated at 2,250 units. In humans, fibrinolytic activity persists for 2 to 6 hours.

Fibrinogen and prothrombin levels are depressed by the administration of fibrinolysin in humans. In a series of 20 patients, no hemorrhagic phenomena were observed. The use of plasmin in amounts of 100,000 to 150,000 units per hour is recommended when total lysis of a thrombus is highly important.

—*Carl H. Calman, M.D.*

Prophylaxis and Treatment of Thrombophlebitis Without Anticoagulants (Zur Verhuetung und Behandlung der Thrombophlebitis ohne Gerinnungskontrolle). W. BIRKENFELD. *Zbl. Chir.*, Leipzig, 1960, 85:1819.

THE AUTHOR BELIEVES that in medical practice with lack of laboratory facilities anticoagulants are not advisable for either therapy or prophylaxis. The author recommends liver preparations given intramuscularly, elastic bandages, and various ointments. Even though many ambulatory patients with thrombophlebitis had a smooth and speedy recovery, the author observed failures such as development of edema, extensive varices, pain, and trophic ulcers. Half of the patients were back to their respective occupations within 11 days, another 25 per cent in 4 weeks.

—*Karel B. Absolon, M.D.*

The Stimulus to Collateral Circulation. H. T. JOHN and RICHARD WARREN. *Surgery*, 1961, 49: 14.

THE GROWTH of the collateral circulation can be divided into 2 phases: that which occurs in the first minutes after arterial block and permits survival of the part and that which proceeds slowly over the ensuing weeks and months and allows function to improve. Mechanisms responsible for the long term increased caliber of the collateral vessels have not been extensively studied. The authors report observations on the effect of pressure gradient, abolition of the pressure gradient, anoxia, amputation, and immobilization on the collateral circulation around a block in the canine femoral artery in the period immediately after occlusion and at intervals of up to 4 months afterward. Eighty-four experiments were performed on 49 dogs. Collateral circulation after occlusion of the superficial femoral artery was measured by pressure recordings, arteriography, and venous occlusion plethysmography.

After femoral artery occlusion there is a rapid fall of pressure followed by a rapid rise with return of some pulsation. This rise continues until the preocclusion diastolic pressure is reached and requires a period varying from a few hours to days. Amputation and immobilization of a limb do not affect the return of pressure or the collateral development in the acute phase but do lead to diminished development in the long term phase. Muscle stimulation in the limb causes a fall in pressure below the block with an increase in pressure gradient. The stimulus to the development of collateral circulation around a block appears to be this pressure gradient between the arteries proximal and distal to the block. Increased flow and dilatation of the vessels follow. The pressure gradient is small in the late phase but is increased in the initial phase of muscle activity, resulting in intermittent collateral vessel dilatation in the months that follow femoral artery ligation. —*Allan D. Callow, M.D.*

Arterioplasty for Severe Ischemia of the Lower Limbs: Indications and Results. D. EMERICK SZILAGYI, ROGER F. SMITH, and ALI ESFAHANI. *Surgery*, 1961, 49: 242.

THE AUTHORS REVIEW their experience with 130 angioplastic procedures performed on 108 patients with severe ischemia of the lower limbs. All patients had pain at rest and local tissue changes including dusky discoloration, dependent rubor, elevation pallor, and atrophy of the skin. All patients were studied with angiograms before and after operation.

A single occlusive lesion was never noted to cause severe rest ischemia. The ischemic manifestations could be placed into 3 groups of increasing severity: (1) severe rest pain and pregangrenous tissue changes; (2) severe rest pain and localized deep gangrene or skin ulceration; and (3) extensive deep gangrene. It is patients with the first two manifestations who comprise the subjects of this study.

When multiple occlusive lesions are present, the development of collateral circulation is progressively more and more deficient distally. The most commonly seen combination is a segmental occlusion of the superficial femoral artery and one or more of the branches of the popliteal artery. Peripheral ischemia caused by occlusive arterial disease of sudden onset is

regarded as a clinical situation of urgent and often emergency character. However, in most cases compensatory collateral circulation prevents tissue death. In only 10 to 20 per cent of instances will ischemia result in gangrene unless the obstruction is relieved. An attempt at immediate operative correction of all such lesions has been found to be unsatisfactory. First, adequate angiographic visualization of the occlusive arterial lesion immediately after acute onset, without which a rational plan of operation is difficult, carries an increased risk. Second, the success of the corrective surgical procedure is diminished by the absence of collateral arterial pathways at this stage. Third, the patient in the midst of the vascular accident is not an ideal subject for a major surgical procedure. During the period of observation, the interruption of a lumbar sympathetic chain by local anesthetic agents is very useful.

Once the threat of tissue death has passed, a period of 3 to 7 days is allowed for the collateral arterial compensation; when it becomes well established the occlusive process is investigated with angiography. If the arterial pattern permits an angioplastic correction, the appropriate surgical procedure is performed. If, after the sudden onset of thrombosis, the ischemia of the limb fails to improve to the degree that is necessary for tissue viability in spite of auxiliary measures, operative treatment is undertaken. The motor function of the small muscles of the feet are used to assess the degree of ischemia. If this function remains, the ischemia has not reached the stage at which tissue death threatens. In cases of ischemia of insidious development, there is no therapeutic urgency and a planned routine is followed. This routine includes assessment of the total patient for operative risk and the careful roentgenographic visualization of the abdominal aorta and its peripheral branches as far distally as the division of the popliteal artery.

The minimum technical requirement for femoropopliteal grafting is the presence of an open popliteal arterial stem with at least one functioning end for a popliteal branch. The minimum technical requirement for aortoiliac grafting is a functional common femoral arterial segment or the existence of an anatomic situation in the popliteal area as described.

An unsuccessful operation may precipitate amputation, but under the operative indications described such an amputation either is inevitable or merely means the loss of a functionless limb.

—Lloyd D. MacLean, M.D.

Effect of Induced Arteriovenous Fistula on Leg Length: 10 Year Observations. Joseph M. Janes and W. Kenneth Jennings, Jr. *Proc. Mayo Clin.*, 1961, 36: 1.

Experimental work had indicated that the length of the leg could be increased in most immature dogs by induction of an arteriovenous fistula between the external iliac vessels. The procedure was then applied to 53 children with a shortened lower extremity. In 11 patients, or 21 per cent, creation of the fistula (femoral) has been too recent—1.5 years or less—for proper evaluation. On the basis of 42 patients, 72 per cent have experienced either a decrease or no change in the discrepancy in length of the two legs, whereas 28 per cent have had an increase in the discrepancy. The maximal amount of discrepancy in length of the two legs that has been overcome over a 4 year period has been 4 cm.

In 14 patients whose fistulas have been closed, the leg lengths became equal in 4, the discrepancy was reduced in 4, and the discrepancy was increased in 6. It would appear from this study that the fistula should preferably be induced between the ages of 8 and 10 years, and that it should be allowed to run 4 to 6 years, provided there are no cardiac or local indications for its closure.

To date, none of the fistulas have had to be repaired because of actual cardiac complications. Complications so far have been the spontaneous closure of 2 of the fistulas. In each instance a new fistula has been created which has functioned satisfactorily.

Although this report covers a 10 year period of observation, it is emphasized that final assessment of the method must still be held in abeyance. The technical difficulty of closing the fistula may be such as to render the method unjustifiable, considering the amount of equalization in leg length that may be expected.

Variations in Blood Pressure and Pulse Rate with Creation or Closure of Arteriovenous Fistulas in Children. W. Kenneth Jennings, Jr., and Joseph M. Janes. *Proc. Mayo Clinic*, 1961, 36: 62.

The authors conclude three things from this study. (1) When an arteriovenous fistula is closed in the human being, there is a predictable fall in pulse rate as well as a rise in the diastolic blood pressure. The response of the systolic pressure in the present study varied and this variation is recorded as the result of homeostatic mechanisms rapidly modifying an initial rise. (2) When an arteriovenous fistula is created, a variable response in blood pressure occurs. This variation is also regarded as the result of homeostatic mechanisms, this time rectifying an initial fall. The pulse rate varies inversely with the blood pressure. (3) The most significant clinical conclusion is that when fistulas of the size used in this study, 0.5 inch, are created in the femoral vessels of children of the age group 4 to 13 years, no significant early changes in blood pressure or pulse rate are produced.

Peripheral Arteriovenous Shunts. H. B. Wulff and Oddvar Eiken. *Acta chir. scand.*, 1960, 120: 12.

The authors report their experience with arteriovenous shunts from 1952 to 1960. They divide the types of shunts into (1) congenital, which occur predominantly in the extremities, cerebral circulation, lungs, and skeletal system, and (2) acquired, which are caused by arteriosclerosis, lues, vascular tumors, or trauma, including surgical trauma, as, for example, during nephrectomy.

The embryology of the vascular system is discussed with regard to the development of congenital shunts, and the pathogenesis of acquired fistulas is described.

Eight cases of arteriovenous shunts are presented. Five of the shunts were due to trauma, and 1 was due to metastatic tumor of bone. The remaining 2 cases were congenital; in 1 of these there was a shunt in the left lung and in the other, a shunt in an extremity.

The signs and symptoms of arteriovenous shunts include local pain, swelling, bruits, and fremitus. If a shunt is present in an extremity before epiphysial ossification, the extremity may increase in length. An additional load is placed on the heart, and diastolic pressure falls because of a decrease in peripheral resistance. The pulse rate rises and blood volumes and cardiac output increase. With this increasing load the heart may fail.

The authors conclude that early operation is advisable to prevent the systemic sequelae of arteriovenous shunts. —*Richard E. Gardner, M.D.*

Regeneration of the Wall of Large Veins with Different Grafts. I. CSILLAG and H. JELLINEK. *Acta chir. acad. sc. hung.*, 1960, 1: 375.

THE AUTHORS DEVISED many experiments to determine what tissues and organs could be used to repair large defects in large veins.

The first experiments involved covering the defects with a loop of small intestine which, though attached to the vessel wall, was nevertheless allowed to retain its original function. They noted that this temporary covering of the gap enabled the vessel wall to regenerate. The process of regeneration began with the organization of the thrombus which had developed in the groove between the vessel wall and the serosa of the attached small intestine. The newly formed vessel wall was inferior to the old one inasmuch as it contained neither elastic fibers nor smooth muscle elements.

After demonstrating that defects of large veins can be repaired by covering them with a portion of small intestine, the authors studied the possibility of using other organs for autoplasty. Several abdominal organs, namely, the stomach, pancreas, spleen, kidney, and uterus proved suitable for insuring the temporary continuity of the inferior vena cava and so making vascular regeneration possible. The newly formed vein wall was similar to that observed with the use of small intestine.

Encouraged by these results they made similar experiments in the thorax where venous defects were covered with pulmonary tissue. Although the adjacent regions of the lung became atelectatic, the lumen of the vein remained open and its wall regenerated as in the other cases.

The authors also determined that vein wall defects regenerate if covered with homoplastic or heteroplastic tissue and that regeneration will occur likewise after using alloplastic substances or even plant tissues.

Attempts to repair defects in the aorta using the same techniques proved unsatisfactory.

—*Ely Elliott Lazarus, M.D.*

Raynaud's Disease with Sclerodactylia. RICHARD G. FARMER, RAY W. GIFFORD, JR., and EDGAR A. HINES, JR. *Circulation*, 1961, 23: 13.

THE RECORDS of 71 patients with Raynaud's disease and sclerodactylia seen at the Mayo Clinic were studied. Follow-up information was obtained for all, over periods varying from 1 to 31 years. Systemic scleroderma seemed to have developed in only 3 patients. Six patients had died but none from systemic scleroderma.

This study does not support the belief that systemic scleroderma and sclerodactylia secondary to Raynaud's disease are the same disease.

SURGICAL MANAGEMENT

PREOPERATIVE AND POSTOPERATIVE CARE

Conjugated 17-Hydroxycorticosteroids in Plasma: Measurement and Significance in Relation to Surgical Trauma. RICHARD W. STEENBURG, LOUIS L. SMITH, and FRANCIS D. MOORE. *J. Clin. Endocr.*, 1961, 21: 39.

A MODIFICATION of the technique of Nelson and Samuels for the measurement of 17-hydroxycorticosteroids was used to determine the level of the free and conjugated form in man and dogs. The response of the serum free and conjugated 17-hydroxycorticosteroids in normal subjects given a maximal adrenal stimulation with ACTH was compared to the response in patients undergoing subtotal gastrectomy. The rise in the level of free 17-hydroxycorticosteroids was greater in the patients undergoing gastrectomy than it was in the normal subjects undergoing adrenal stimulation with ACTH. Conversely, the rise in the serum levels of 17-hydroxycorticosteroids was more gradual in the patients undergoing gastrectomy. These differences were not significant.

In adrenalectomized dogs given a constant intravenous infusion of hydrocortisone, laparotomy caused a rise in the serum level of 17-hydroxycorticosteroids. The serum level of the conjugates did not fall as would be expected, but instead remained the same or increased. —*John H. Davis, M.D.*

The Heparin Tolerance Test and Thromboembolic Incidence in Surgery. J. GORMSEN and B. FL. HAXHOLDT. *Acta chir. scand.*, 1960, 120: 121.

THE CONTINUING SEARCH for ways to predict venous thromboembolic disease in patients undergoing operation or to make early diagnosis when venous thrombosis occurs indicates the lack of a good method. These authors have investigated a test for heparin tolerance, measuring coagulation after adding heparin to the patient's blood. They found that patients in whom thrombosis developed later and who suffered pulmonary embolism did have increased tolerance for heparin. But so had many others who had no such complications. They question whether or not the latter patients have a better mechanism of thrombolysis.

Also, the heparin tolerance is increased in some patients with malignant diseases and to a lesser degree in patients with chronic infection. Yet, in the elderly patients, as a category reported to have higher incidence of postoperative venous thrombosis, the heparin tolerance is not significantly increased.

—*Leonard D. Rosenman, M.D.*

Intravenous Nutrition. RAYMOND E. WESTON and S. JEROME PORT. *California M.*, 1961, 94:20.

WITH the available parenteral solutions and supplements now in use, it is possible to treat, prophylactically or actively, most of the common fluid and electrolyte aberrations. Concentrated glucose solutions given intravenously often produce severe phlebitis and thrombosis. Therefore, highly concentrated dextrose solutions have not been given intravenously except, as in patients with acute renal failure, by way of plastic catheters threaded through extremity veins into the vena cava. Some investigators have emphasized the dangers of thrombophlebitis after this practice, or of septicemia if there is severe infection elsewhere in the body.

The authors have produced a solution of 50 per cent dextrose in water, containing 1 mgm. of hydrocortisone per 100 ml., which they have used successfully in 70 patients for intravenous nutritional maintenance and repletion. There were no adverse systemic effects during or after 216 infusions. The only undesirable local reaction was the rare occurrence of pain in the arm when concentrated solutions were given too rapidly. Glycosuria was minimal if the infusion rate did not exceed 0.85 gm. of glucose/kgm. of body weight per hour, particularly if 50 units of insulin was added to each 550 ml. bottle of 50 per cent dextrose. In patients without significantly elevated serum potassium content, 30 mEq. of potassium chloride, acetate, or phosphate was added to each bottle to prevent hypokalemia.

The absence of significant local reaction to accidental subcutaneous infiltration of the 50 per cent dextrose solution with hydrocortisone was noted and was believed to be consistent with the anticipated anti-inflammatory properties of the steroid. The failure of the steroid to reduce the incidence of phlebitis and thrombosis after infusions of more than 24 to 48 hours' duration was not surprising to the authors, their belief being that the time-intensity factor far exceeds the physiologic-pharmacologic potential of the hydrocortisone.

The authors emphasize that these observations are preliminary and stress that further studies on the clinical and metabolic effects of such treatment are in progress. —*Gordon F. Madding, M.D.*

WOUNDS AND THERMAL INJURIES

Experiences in the Management of the Burn Wound. TRUMAN G. BLOCKER, JR., STEPHEN R. LEWIS, D. A. GRANT, VIRGINIA BLOCKER, and J. E. BENNETT. *Plastic & Reconstr. Surg.*, 1960, 26: 579.

THE EXPERIENCES WITH and the lessons learned from the treatment of 1,200 burned patients form the basis of this report. Clinical investigation of these patients is started as soon as they are admitted and is followed up in the operating room and the ward.

The exposure method of treatment has been studied and found to be an effective one. The limitations, indications, and contraindications are discussed.

The use of topical analgesics and enzyme debriding agents has been evaluated but as yet none has been found to be completely satisfactory in clinical use.

The management of the acute burn is discussed in detail relative to practical methods. The burn wound is disturbed as little as possible except to remove gross

dirt. The exposure technique is used as a general rule and special equipment such as Stryker or Foster frames and the Circa bed are employed when needed.

The hands and certain other areas are always dressed, using a grease base covered with layered gauze held in place with a kerlix gauze roll. Hands are carefully dressed in the position of function.

Seven to 10 days postburn the patient is re-evaluated, with respect to the burn wound, in the operating room under nitrous oxide anesthesia. An initial debridement is accomplished at this time and the patient is again exposed or dressed as necessary. This procedure is repeated every 3 days until the burns are healed or the eschars have separated and the patient is ready for grafting.

When the areas of full thickness burn are ready for grafting the patient is anesthetized, cleansed, and grafted with split thickness grafts. The donor sites are covered with a single layer of fine-mesh glycerinized gauze and the grafted areas are left exposed. Remaining areas of granulation tissue are dressed with compression bandages until they are ready for grafting.

When the patients are nearly covered with skin grafts, daily tub baths and extensive physiotherapy are instituted. —*John H. Davis, M.D.*

INFECTIONS AND ANTIBIOTICS

Penicillinase in Penicillin Reactions. JOHN C. TRINCA and THOMAS E. B. KEEN. *Med. J. Australia*, 1960, 2: 973.

A WIDE VARIETY of signs and symptoms accompanies the allergic reactions which may follow the administration of penicillin. In general, the reactions may be divided into two main groups—(a) immediate, of the anaphylactic type, and (b) delayed, of a serum sickness type. A certain amount of overlap between the two groups may occur.

The fact that penicillinase can convert penicillin in vitro into nonantigenic penicilloic acid suggests that it may be of considerable value in the management of penicillin reactions. Between March 1959 and March 1960, penicillinase was administered by intramuscular injection to 40 patients in doses ranging from 350,000 to 800,000 units. All of them had been suffering from an irritating skin condition believed to be caused by penicillin. The chronicity of the skin condition varied greatly from 1 day to 2 years. An urticarious eruption was the predominant feature in 31 cases. Three of the cases were later diagnosed, with the result that penicillin was discounted as an etiologic factor.

After treatment with penicillinase, 20 of the patients were improved, but the remainder showed no response. Thirty-one of the 40 patients received a single injection of penicillinase, 7 received two injections, and 2 received three.

In several of the cases treatment with antihistamines and corticosteroids was concurrently carried out, so evaluation of the effectiveness of penicillinase treatment was difficult. In some instances there was no certainty that penicillin was the sensitizing agent. A control series was not run. No immediate reactions of the anaphylactic type were encountered during this study. —*Bernard C. Gerber, M.D.*

A New Antistaphylococcal Penicillin, BRL 1241 (Une nouvelle pénicilline électivement active sur le staphylocoque). MAURICE PESTEL. *Presse méd.*, 1960, 68: 2083.

THE PRODUCTION by fermentation and isolation of the basic molecule of penicillin, 6-aminopenicillanic acid, has made possible a new series of biosynthetic penicillins by introducing side chains into the basic molecule. One of these biosynthetic penicillins, 2-6 dimethoxybenzamidopenicillin sodium, celbenin, known in this country as staphcillin, is remarkable in that it is bactericidal against staphylococci resistant to other antibiotics. This effect is due to the dual action of the new biosynthetic penicillin: intrinsic bactericidal properties and the capacity to resist destruction by the enzyme penicillinase.

The bactericidal action of the new penicillin is much inferior to that of the old aqueous penicillin G on a weight-for-weight basis. As with the old benzylpenicillin, celbenin (staphcillin) must be given by injection, is rapidly eliminated from the blood stream, and requires a minimum of four 6-hourly intramuscular injections a day in adults for therapeutic effect. Individuals allergic to older penicillins are allergic to the new compound. Injections are not painless, and prolonged treatment may evoke painful indurations.

The principal indication for celbenin (staphcillin) is severe, invasive, penicillin-resistant staphylococcal sepsis. Therapeutic trials have confirmed its efficacy in a variety of severe staphylococcal diseases. Like the staphylococcus, other micrococci such as pneumococci and streptococci are less susceptible to the new than to the old penicillin, so that the major therapeutic indication is staphylococcal disease due to organisms resistant to other antibiotics.

—*Edwin J. Pulaski, M.D.*

The Absorption and Excretion of N-(Pyrrolidinomethyl) Tetracycline. G. A. CRONK, F. H. BUCKWALTER, W. B. WHEATLEY, and H. ALBRIGHT. *Am. J. M. Sc.*, 1961, 241: 1.

SINGLE intramuscular injections of 143 mgm. of N-(pyrrolidinomethyl) tetracycline in healthy volunteer adults produced an average serum concentration of 1.56 μg. per ml. in 1 hour. This dropped to 0.81 in 8 hours and to 0 in 24 hours. Larger doses gave correspondingly higher levels, the largest test dose being 786 mgm., which produced a high level of 11.5 μg. per ml. in 1 hour, dropped to 5.51 in 8 hours, and to 1.79 in 24 hours.

In multiple dose experiments, blood levels were checked just before and 1 hour after each dose. With a dosage of 178 mgm. every 12 hours, there was no progressive increase in either the high or low levels attained. That is, there was no accumulation of the antibiotic. The same dose given at 8-hour intervals produced a gradual increase in the blood levels with each successive dose. When a dosage of 191.5 mgm. was used, neither the 12-hour nor 24-hour schedules showed significant accumulation. With a dose of 393 mgm., a stable level was maintained with injections every 24 hours. On a 12-hour schedule, a cumulative effect was observed, and on an 8-hour schedule, this effect was even more pronounced than on the former schedule.

Between 50 and 60 per cent of the intramuscular tetracycline was excreted in the urine during the first 30 hours after any size dose.

Injection of N-(pyrrolidinomethyl) tetracycline combined with 40 mgm. of lidocaine caused little discomfort during injection. There was moderately severe discomfort 20 minutes later, lasting 1.5 to 2.5 hours. There was no apparent residual tissue reaction. Considerably greater pain occurred if the antibiotic was given without lidocaine. No other undesirable side effects were observed.

—*Stanley W. Tuell, M.D.*

HYPOTHERMIA

Artificial Hypothermia by Insufflation of Cooled Gases Intratracheally. A. J. Dhruva, P. K. Sen, and G. B. Parulkar. *J. Postgrad. M.*, Bombay, 1960, 6: 170.

These experiments suggest that cold gases delivered to the lung by endotracheal tube can cool the experimental animal slowly to a moderate hypothermia of 33 degrees C. in 2 or more hours. However, a significant number of dogs suffer injury to the lungs if the temperature of the inhalant is 11 degrees C. Further studies are in progress.

—*Leonard D. Rosenman, M.D.*

Profound Hypothermia and Complete Circulation Interruption. William E. Neville, Shinobu Kameya, Mustafa Oz, Byron Bloor, and George H. A. Clowes, Jr. *Arch. Surg.*, 1961, 82: 108.

Hypothermia in conjunction with perfusion by a pump oxygenator combines the benefits derived from a reduction in the metabolic demands of the tissues with the ability to adequately perfuse the entire organism. The heart ceases to function at temperatures below 25 degrees C. Not only is a further reduction in body temperature permissible, but rewarming is not difficult. The authors present data concerning the metabolic effects of profound hypothermia induced by perfusion, and the additional alterations caused by total arrest of the circulation at temperatures near 10 degrees C.

Hemodynamics. As the animal or patient is cooled by perfusion to 30 degrees C., a rise in peripheral vascular resistance occurs. Thereafter there is a gradual decline in blood pressure and an apparent fall in the total peripheral resistance combined with a rise in blood viscosity. As the body temperature is lowered, a gradual decrease in venous drainage into the venous reservoir is evident. The perfusion rate must be decreased or extra blood must be added to the extracorporeal circuit to maintain a constant flow rate. Upon rewarming, the blood volume increases in the extracorporeal circuit and the estimated intracorporeal blood volume returns toward normal. The shift amounts to about 4.9 per cent of body weight.

Oxygen consumption. Oxygen is extracted from the blood in proportion to the duration of circulatory arrest and the temperature gradients within the body. Consumption falls with body temperature, reaching one-sixth of normal at 10 degrees C. Consumption falls with decreasing perfusion rates, and at 10 degrees is maximal with a rate of 60 c.c./kgm. Consumption is higher when esophageal and rectal temperatures are not in equilibrium.

Lactic acid production. Lactic acid increases during perfusion and is 60 per cent above initial values after rewarming to 30 degrees C.

Hydrogen ion concentration. *p*H falls during perfusion and rises with rewarming and restoration of circulation. When circulation is interrupted for 15 to 30 minutes *p*H values are not significantly different from those of animals whose circulation was not completely interrupted. When circulation is interrupted for longer periods, 30 to 78 minutes, the animals are alkalotic immediately after arrest but become profoundly acidotic as rewarming progresses.

Mortality and pathologic findings. Of 45 animals, all survived perfusion and profound hypothermia, but the short term mortality was high among 32 animals cooled by partial cardiopulmonary bypass—15 of the 32 animals. In those cooled with total bypass, only 2 of 10 survived. In animals that died shortly after perfusion there was marked pulmonary edema. This increased in severity with the passage of time, and alveolar spaces after 6 to 12 hours were completely filled with blood. Subendocardial hemorrhage was also found.

Clinical experience. Operations on 47 patients are reviewed, 10 of the patients being perfused at temperatures of 20 to 25 degrees C. Two deaths were attributed to the perfusion, in 1 case the pulmonary parenchyma being destroyed by the high-pressure perfusion of the lungs through a large patent ductus. One patient was cooled to 10 degrees in a perfusion lasting 3 hours and 58 minutes. The lowest human temperature was 8 degrees. Three of 4 patients survived cooling below 20 degrees C.

—*Carl H. Calman, M.D.*

Hypothermia by Intraperitoneal Route; Experimental Data (L'hypothermie par voie intra-péritonéale). J. Descotes, M. Tanche, and J. Chatonnet. *Ann. chir.*, Par., 1960, 14: 1525.

This is an experimental study from the Surgical Clinic and the Institute of Physiology of the University of Lyon, Lyon, France on a new and simple method of internal cooling. The authors have employed the extraperitoneal approach in an endeavor to avail themselves of the large peritoneal surface as an efficient heat exchanger. In 5 dogs cooling was obtained by perfusing the peritoneal cavity with saline solution at 4 degrees C. by way of two multiperforated drains introduced through two stab wounds. The perfusing solution, at a rate of 150 to 200 c.c. per minute, enters the abdomen by way of the subhepatic drain and escapes by gravity through the drain in the lower abdomen. About 1 to 2 liters of saline are perfused in 10 to 12 minutes. The temperature of the escaping fluid is, on the average, 22 degrees C. In 13 dogs cooling was obtained by pouring saline solution at 4 degrees C. into the peritoneal cavity through a midline laparotomy. After a 5 minute period, the solution, now at a temperature of 22 to 25 degrees C., has to be changed in order to re-establish an efficient thermic gradient. A temperature of 30 degrees C. is achieved in about 15 minutes. The remarkable aspects of intraperitoneal cooling are: (1) simplicity; (2) instantaneousness, the

esophageal temperature dropping 1 degree C. in 2 minutes after a latent period of less than 1 minute; and (3), rapidity, the rate of cooling being, on the average, 0.3 to 0.5 degrees C. per minute.

The temperature gradient of the extra-abdominal organs is not very important since the distribution of the cooling seems to be rather homogeneous.

In their experiments the authors have noted the absence of cardiovascular, respiratory, humoral, and histologic changes. They believe that this type of cooling is superior to surface cooling chiefly because it can be easily improvised when the need arises during a laparotomy. The only item necessary is from 7 to 10 quarts of sterile normal saline solution stored in a refrigerator. In 15 minutes during a laparotomy, it is possible to lower the temperature of an adult patient to 30 degrees C. This is made easier by the fact that a certain degree of hypothermia, up to 34 to 35 degrees C., is achieved by the act of exposing the peritoneum and the intestinal mass to the external environment. Hypothermia of 28 to 30 degrees C. permits an increase to twice the time of the safe clamping of certain vessels such as the renal artery, the portal vein, and mesenteric vessels. It is possible to lower the temperature into the range of deep hypothermia—below 20 degrees C.— with this method. The procedure, however, becomes very slow because the thermic gradient obviously becomes inefficient and, above all, the cardiac output decreases at low temperatures. —*Michele A. Chiechi, M.D.*

EXTRACORPOREAL CIRCULATION

Experimental Study on Peripheral Circulation During Extracorporeal Circulation, with a Special Reference to a Comparison of Pulsatile Flow with Nonpulsatile Flow. JUN TAKEDA. *Arch. jap. Chir.*, 1960, 29: 1407.

THE EFFECTS on peripheral circulation of pulsatile and of nonpulsatile flow in extracorporeal circulation were studied in dogs. With nonpulsatile flow, 10 to 15 minutes after onset of extracorporeal circulation, the flow rate in true capillaries slowed down and finally stopped. Blood flowed mainly through preferential channels and arteriovenous anastomoses; also, edema occurred in tissues especially in the abdominal region after 10 to 20 minutes of extracorporeal circulation.

Arterial blood pressure, peripheral vascular tone, and normal peripheral circulation were more difficult to maintain in the nonpulsatile cases than in the pulsatile cases, because the peripheral vascular tone especially in the downstream flow of small arteries decreased in the nonpulsatile cases.

From these results, the author concludes that it is necessary to maintain pulsatile flow in the extracorporeal circulation of long duration, because nonpulsatile flow causes marked changes in the peripheral circulation. —*Harold Laufman, M.D.*

Hemodynamic Studies on Extracorporeal Circulation with Pulsatile and Nonpulsatile Blood Flows. AKIRA NONOYAMA. *Arch. jap. Chir.*, 1960, 29: 1381.

THE EFFECTIVENESS of a pulsatile and nonpulsatile blood flow in extracorporeal circulation was studied experimentally in dogs. Each group was maintained for a period of 60 to 90 minutes of total body perfusion. Arterial pressure was easily maintained in the pulsatile group and was kept about 15 mm. Hg higher on the average than that of the nonpulsatile group under the same flow rate. Consequently, if the arterial pressure of over 80 mm. Hg was desired, the pulsatile group needed a flow rate of 70 c.c./kgm./minutes, while a flow rate as great as 90 c.c./kgm./minutes was necessary in the nonpulsatile group. Peripheral resistance began to decrease within 20 minutes and gradually fell in the course of perfusion in the nonpulsatile group. Central venous pressure did not differ markedly in either group but, from the results of changes in body weight and venous hematocrit value, the blood pooling seemed to occur during perfusion in the nonpulsatile group.

In the pulsatile group, oxygen consumption maintained almost normal levels throughout the total bypass, while in the nonpulsatile group it fell gradually in the course of perfusion. In the nonpulsatile group *p*H fell to 7.10 one hour after onset of perfusion, and marked metabolic acidosis was noted. In both groups, no direct correlation was noted either between *p*H and flow rate or between *p*H and arterial pressure, but a linear relationship was observed between *p*H and oxygen consumption.

From these results it is concluded that perfusion with pulsatile flow should be a safer procedure when blood flow is below 100 c.c./kgm./minute and particularly when the extracorporeal circulation is continued for more than 30 minutes.

—*Harold Laufman, M.D.*

Clinical Observations on Vasomotor Reflexes in Relation to Blood Volume in Open Heart Surgery. P. G. F. NIXON, V. A. GRIMSHAW, and G. H. WOOLER. *Lancet*, Lond., 1960, 2: 1429.

CLINICAL OBSERVATIONS on 60 patients undergoing open heart operations suggest that vasomotor responses may offer a more reliable guide to blood volume than do the levels of arterial and central venous pressure.

The rapid injection of 80 to 90 ml. of blood into the femoral artery may cause the arterial pressure to fall or to rise. The fall, which is attributed to reflex vasodilation, is associated with unimpaired blood volume. The rise is caused by injection into a constricted arterial bed, and the constriction is associated with hypovolemia. —*Ernest D. Bloomenthal, M.D.*

Intracardiac Surgery with the Aid of the Cardiopulmonary Bypass (Intrakardiale Chirurgie mit Hilfe des extracorporalen Kreislaufs). E. S. BÜCHERL, F. LINDER, G. RÜCKER, and K. J. SCHMUTZER. *Langenbecks Arch. klin. Chir.*, 1960, 294:379.

THE AUTHORS REPORT on 120 patients operated on since 1958. A modified Mark-Gibbon oxygenator was utilized in the first cases, but the Kay and Cross modification of the Bjork apparatus is preferred at the present time. Fifteen cases of secundum type atrial defects were treated by direct closure; in the primum type and atrioventricularis communis defects an artificial prosthetic ivalon patch was used in most cases for closure. A similar technique was applied for closure of interventricular defects.

The other types of cardiac anomalies treated were aortic stenosis, valvular or infundibular pulmonary stenosis, and Fallot's tetralogy and pentalogy. The highest mortality was in the last group of patients, namely, 9 of 17 cases. All patients operated on for pulmonary stenosis survived. The other cardiac anomalies treated included mitral insufficiencies, aortic aneurysms, aortic-pulmonary windows, corrected transpositions, and multiple anomalies.

The following complications were registered in 100 patients: pulmonary complications in 30 (pneumonia, pulmonary edema, atelectasis, empyema), and cardiac insufficiency in 20 (cardiac arrhythmias in 4, cardiac arrest in 3 patients, pericardial tamponade in 1 case, emboli in 6). Twenty-nine patients bled excessively and 24 had wound infections. The authors believe that hypothermia per se is hardly ever indicated. Cardiac bypass at normal temperatures is satisfactory for perfusions up to 1 hour. For longer periods of cardiac bypass, hypothermia added to perfusion presents significant advantages.

—Karel B. Absolon, M.D.

ANESTHESIA

Experimental and Clinical Study of a Metabolically Active Substance with Central Inhibitory Action; Sodium 4-Hydroxybutyrate (Sur un substrat métabolique à action centrale inhibitrice). H. LABORIT, J.-M. JOUANY, J. GERARD, and F. FABIANI. *Presse méd.*, Par., 1960, 68: 1867.

SODIUM 4-HYDROXYBUTYRATE has been found to have some interesting properties which may lend themselves to better anesthesia and also to use in psychiatry.

Doses from 0.5 to 8 gm./kgm. of body weight have been used to anesthetize laboratory animals. Even though the drug is administered intravenously, the animal does not go to sleep for 10 to 15 minutes, the process resembling natural sleep. If the animal is held in restraints it does not go to sleep at all; but, if released, it will fall asleep in 30 minutes and can be operated upon.

It has been determined that 0.06 gm./kgm. is an adequate anesthetic dose for man. Premedication with meperidine hydrochloride and promethazine makes induction certain. Good muscle relaxation is obtained. The metabolic rate is not altered. There is a slight tendency for the body temperature to fall. It has been used successfully in hypothermia without resultant shivering. The heart beat slows slightly and the blood pressure remains constant or rises slightly. Respiration slows and may take on a Cheyne-Stokes character.

Electroencephalographically, there is a flattening of the alpha rhythm and the appearance of slow waves. No spindles are seen. Arousal patterns are normal. *—George L. Potter, M.D.*

Progressive Loss of Protective Reflexes in the Airway with the Advance of Age. HENNING PONTOPPIDAN and HENRY K. BEECHER. *J. Am. M. Ass.*, 1960, 174: 2209.

THE PROTECTIVE REFLEXES of the airway were investigated with correlation of advancing age and the progressive decrease in the acuity of perception and reflex activity. The temporary closure of the vocal cords and cessation of respiration is the reflex elicited by agents, either mechanical or chemical, which are noxious to the respiratory tract. This reflex, the Kratschmer reflex, forms the basis for the present study in which the threshold response to the administration of 1.6 per cent ammonia gas is measured in 103 healthy male volunteers ranging in age from 15 to 84 years. The respirations and end point were recorded on a metabolic spirometer modified to serve as a nonrebreathing system.

Subjects were divided into groups according to age. There is a marked lessening of the irritability of the upper airway with ageing. The median threshold increases almost 6 fold, the steepest change taking place after middle age. Ageing is also noted to be accompanied by an increasing variability in individual sensitivity. The reason for the increased variability is not known.

In subjects retested at later dates the threshold is consistent and reproducible. The consistency of the method used is supported by comparison with the results of other workers.

The loss of protective reflexes of the airway is probably the result of degenerative changes of the nervous system at all levels rather than any specific degenerative process. The increased incidence of bronchitis, pneumonitis, silent tracheal aspiration, and other respiratory complications in the elderly may be explained by the progressive loss of the protective reflexes of the airway. Injudicious use of depressant drugs in the elderly may induce problems not present in younger persons. *—Patrick F. Jewell, M.D.*

Hydroxydione as a General Anesthetic in Gynecology and Obstetrics (Hydroxydion als Vollnarkotikum in der Gynaekologie und Geburtshilfe). R. MARTIN, K.-H. HARRICHHAUSEN, and K.-H. SPONER. *Geburtsh. & Frauenh.*, 1960, 20: 1242.

HYDROXYDIONE, 21-hydroxy-pregnane-3, 20-dione-sodium-hemisuccinate, is a further development from those steroids, such as desoxycorticosterone and progesterone, which have narcotic properties in large doses. This substance no longer has any hormonal effect and is marketed as a narcotic. This is probably the first report of the use of this drug as the sole anesthetic agent without supplementary ether or nitrous oxide in gynecologic surgery.

Premedication includes "megaphen," "atosil," and demerol, and hydroxydione is used as a 5 per cent solution in normal saline by intravenous application. The usual dose is 1 gm., although one of 2 gm. is still safe, given as a single injection in which the speed determines the depth and the amount the length of the anesthesia. The entry and exit were gradual and mild, and retrograde amnesia was frequently reported. The anesthesia appeared to be safe in 4 patients with diabetes, 41 with myocardial ischemia, 16 with anemia, and 1 with eclampsia in a group of 500 cases. Since the blood level in the fetal circulation was much lower than that in the maternal system the agent seemed to be ideal for cesarean section, and in 40 such cases only the premedication seemed to have an effect on the infant's condition.

There were 3 instances of respiratory depression, 79 of circulatory depression, 25 instances of local phlebitis, and 1 of gangrene of the hand, probably the result of intra-arterial injection. The last case is reported in detail. There were 9 deaths, none of them attributable to the anesthetic. The authors consider this drug the most practical and innocuous narcotic agent in gynecology. —*W. Dieter Bergman, M.D.*

Clinical and Experimental Criteria on the Use of Anesthesia in Protracted Pregnancy (Criteri orientativi clinico-sperimentali, per l'anestesia nella gravidanza protratta). C. BERTONE, I. VOLPI, and L. ALETTI. *Minerva gin.*, Tor., 1960, 12:1115.

THE COMPOSITION of the cord blood of babies born after normal pregnancy, physiologic protracted pregnancy, or pathologic protracted pregnancy and of babies delivered by cesarean section was studied at the Department of Obstetrics and Gynecology of the University of Turin Medical School, Italy. In the group delivered by cesarean section, either general anesthesia with cyclopropane and ether, nitrous oxide and ether, or peridural anesthesia was used. A total of 65 venous and arterial blood samples were analyzed for oxygen content and saturation, oxygen-hemoglobin, oxygen arteriovenous difference, and oxygen utilization coefficient. The following results were obtained: the oxygen values were normal in the babies born after normal pregnancy and after physiologic protracted pregnancy. In the latter situation a 90 per cent correlation between clinical evaluation and oxygen values was found. The oxygen values were greatly diminished in the cord of the infants born after pathologic protracted pregnancy or by cesarean section when the mother underwent general anesthesia. No abnormal values were noted in the cord blood of the newborns of mothers subjected to peridural anesthesia.

—*Maria Serratto, M.D.*

Anesthesia for Cleft Lip and Cleft Palate Surgery. JOHN E. MAHAFFEY, J. HENRY SPROUSE, S. M. WITHERSPOON, and CLAUDIA OXNER. *Plastic & Reconstr. Surg.*, 1960, 26:596.

NINETY-ONE cleft palate and cleft lip repairs were performed at the Medical College Hospital, Charleston, South Carolina. The average age of patients with cleft lip repairs was 3 months, and the average age of those with cleft palate repairs was 22 months. A preoperative hemoglobin of less than 10 grams or an upper respiratory infection is considered adequate indication for cancellation of operation.

Preoperative medication consisted of demerol alone, 0.57 mgm. per pound, or with rectal pentothal sodium, 10 mgm. per pound, used in conjunction with scopolamine or atropine, 0.004 mgm. per pound. All operations were performed under endotracheal anesthesia, with a nonrebreathing valve or occasionally an infant circle. In cleft lip repair anesthesia is administered by way of an orotracheal tube and in cleft palate repair by way of a nasotracheal tube. Muscle relaxants were used in 41 per cent of the cases to facilitate intubation. d-Tubocurarine was given in a dose of 0.15 mgm. per pound or succinylcholine in a dosage of 1 mgm. per pound. All patients are ventilated with 100 per cent oxygen before intubation.

The anesthetic agents used were nitrous oxide-fluothane, nitrous oxide-ether, and nitrous oxide-pentothal. The authors believe that although these various agents have been used satisfactorily, the nitrous oxide-fluothane offered some advantages over the two other techniques of anesthesia.

—*Carl Schiller, M.D.*

Safer Intravenous Anesthesia. JOHN W. DUNDEE. *Irish. J. M. Sc.*, 1961, ser. 6: 12.

THIS REPORT is a discussion of the factors concerned with the safety of intravenous anesthesia and reviews the present-day position of the drugs employed in its production. Thiopental and similar agents are most useful drugs, which, however, have a greater inherent toxicity than some of the inhalation agents. Their toxicity is enhanced when they are used as sole anesthetics for other than very brief minor operative procedures.

If one realizes that the intravenous barbiturates are principally hypnotics, that reflex response to stimuli cannot always be abolished with a safe dosage, that the drugs have little analgesic action, that they are direct myocardial depressants, and that they are not rapidly broken down in the body, then they can be used safely for most operative procedures. The present-day trend is to utilize to the maximum less toxic adjuvants, nitrous oxide, intravenous analgesics, and/or muscle relaxants, depending on the circumstances. Each drug in the combination, now known as balanced anesthesia, is used for a specific purpose: narcosis, relaxation, analgesia, or suppression of reflex responses. —*Mary Frances Poe, M.D.*

Control of Postoperative Vomiting with Perphenazine, Trilafon. BJÖRN LIND. *Acta anaesth. scand.*, 1960, 4: 181.

THE ABILITY of perphenazine to reduce postoperative vomiting was studied in 278 consecutive patients operated upon under general anesthesia with nitrous oxide and oxygen combined with ether and/or succinyl choline. Short or minor procedures and emergency operations were not included. Perphenazine or a placebo from coded ampules of identical appearance was given intramuscularly to alternate patients at the conclusion of the operation. The emesis of 50 ml. or more of gastric contents was recorded as vomiting. Nausea was not recorded.

The single injection of 5 mgm. of perphenazine reduced postoperative vomiting by half in the series. The effectiveness exceeded 6 hours and seemed to be sufficient to cover the 24 hour observation period. Hypotension, prolongation of awakening time, and other side effects were not troublesome. The demand for analgesics during the 24 hour period was not reduced, but perphenazine had a marked sedative effect. —*Mary Frances Poe, M.D.*

Anesthetic Accidents. J. B. WYMAN. *Proc. R. Soc. M.*, Lond., 1960, 53: 847.

THE FIRST PRINCIPLE of anesthesia is to check the patient, the machine, and the drugs. The anesthetist should also protect the patient from injuries due to errors in posture. Excessive pressure on thighs and ankles due to prolonged use of unpadded lithotomy

poles should be avoided as should dangling the feet and the arms which may give rise to foot and wrist drop.

The great danger today is that of static electricity initiating an explosion. The elimination of explosions depends on prophylaxis. One should either avoid explosive agents or take all the precautions recommended.

The inhalation of gastric contents is responsible for more anesthetic deaths than any other cause. It is the greatest single cause of maternal mortality during obstetrics. To prevent inhalation of gastric contents during emergency operation one may, when suitable, use spinal, epidural, or local analgesia instead of general anesthesia. If general anesthesia is essential, difficulty may be avoided by waiting if possible until the stomach empties, by emptying the stomach by means of induced vomiting, by using a technique that gives a smooth induction until the vomiting reflex is depressed by deep general anesthesia, and by mechanically preventing gastric contents from entering the trachea. —*Robert A. Nabatoff, M.D.*

INSTRUMENTS AND APPARATUS

Foreign-Body Granuloma Resulting from the Use of Starch Glove Powder at Surgery. ULLA ISING. *Acta chir. scand.*, 1960, 120: 95.

ALTHOUGH not as intensely or frequently as caused by talc, granulomas in tissues which may delay healing or cause other complication can be produced by the starch granules in today's glove powder. The granulomas may caseate and resemble tuberculosis. Ziehl-Neelsen stain colors the starch particles bright red which is a good method for identifying the true cause of the ganulomas. Experimental preparations in rodents reveal similar granulomatosis.

It is clear that surgeons should be careful to avoid contaminating surgical wounds with large amounts of glove powder. —*Leonard D. Rosenman, M.D.*

RADIOLOGY

DIAGNOSTIC ROENTGENOLOGY

Application of High Kilovoltage Technique Utilizing Negative Contrast Media (Anwendung der Hartstrahltechnik, 200 kV, bei Untersuchungen mit negativen Kontrastmitteln). H. ENGELKAMP. *Fortsch. Röntgenstrahl.*, 1960, 93: 230.

ALTHOUGH the advantages of the high kilovoltage technique were recognized as early as 1924, it wasn't until the development of serial exposures that it became a necessary tool. The two important factors were the shorter exposure time and the decreased roentgen-ray tube load.

The advantages of the high kilovoltage technique are listed as follows:

1. Tube life is greatly increased.

2. The penetration is increased so that lower entry doses are required for the same exit dose.

3. One of the important characteristics of hard roentgen rays is the tendency toward retention of mass-absorption coefficients with materials of different atomic weights, so that the contrast between bones and muscles becomes less and less with rising kilovoltage. The contrast between soft tissues and air remains about the same in the 60 to 200 kv. range.

4. A disadvantage of the technique is the increased scatter of roentgen rays which can be limited with the use of grids.

5. The geometric loss of detail which is dependent on the focal spot and tube-target distance can be improved by using large tube-target distances.

The author used the high kilovoltage technique with negative contrast media in areas of overlying bone or when a large target area was desired. The advantages and disadvantages of pneumoencephalography, pneumopyelography, pneumomyelography, and retropneumoperitoneum are discussed. Measurements of the gonadal dose were made and the amounts were lower for the high kilovoltage technique in comparison to the conventional type.

—*George Bonk, M.D.*

Axial Tomography in the Examination of Chest Organs. ESKO TÄHTI and R. STENTRÖM. *Ann. chir. gyn. fenn.*, 1960, 49: 449.

TOMOGRAPHS are generally taken parallel to the longitudinal axis of the body in the frontal and sagittal directions. Axial tomography makes it possible to obtain roentgenograms from thin layers which are crosswise to the patient's longitudinal axis. This report is confined to the discussion of this transverse body section roentgenography or axial tomography.

The authors give a brief review of the history of axial tomography and a brief explanation of the technique which involves the horizontal beam of roentgen rays meeting the patient obliquely at 25 degrees and hitting a horizontally positioned roentgen ray film. This angle of incidence gives some inaccuracy because the image of the point of the layer to be pictured does not fall on the same place in the film and also because this angle of incidence produces a magnification of modest degree. However, real advantages are pointed out by the authors who review a number of specific cases in which the pulmonary lesion is clearly visualized and gives a good idea of the topographic extent of the pulmonary changes and the relation of those changes to the mediastinum and the walls of the thorax. They point out that axial tomography is irreplaceable in directing roentgenotherapy to deep lying pulmonary lesions and in calculating the deep dosage. It is also particularly valuable in assessing deformations of the thorax, e.g., kyphoscoliosis. —*Ward D. O'Sullivan, M.D.*

Phenobutiodil: A New Cholecystographic Medium. DONALD N. DYSART and JOHN S. ALEXANDER. *South. M. J.*, 1961, 54: 57.

THE AUTHORS have reported on 110 cholecystographic examinations performed at the Scott and White Clinic, Temple, Texas, using a new oral cholecystographic medium called phenobutiodil, soon to be marketed under the trade name of vesipaque. These patients were compared with another group of 39 patients in whom cholecystographic examinations were performed with iophenoxic acid, teridax.

Gallbladder visualization was considered satisfactory in 94 per cent of the patients in the vesipaque group as compared with 62 per cent of those in whom teridax was employed. This difference was further emphasized by comparing those in whom an excellent study was obtained: 61 per cent with the new material as compared with 31 per cent with teridax. Visualization of the extrahepatic biliary ducts after a fat meal, seen in only 22 per cent of patients with teridax, was noted in 50 per cent of those with vesipaque.

The administration of vesipaque was associated with minimal and mild side effects. Two of 3 patients had no complaints whatsoever with the use of this preparation. In a previous study, teridax was noted to be much less free of such side effects.

The authors suggest that as experience with this new medium is obtained and comparative studies are made with other cholecystographic media, vesipaque will find considerable acceptance.

—*Harvey N. Lippman, M.D.*

Simultaneous Oral Cholangiography and Cholecystography (Perorale simultane Cholangio- und Cholecystographie). M. SCHACHERL. *Fortsch. Röntgenstrahl.*, 1960, 93: 213.

SIMULTANEOUS oral cholangiography and cholecystography was made possible with the advent of biloptin, a sodium salt of beta (3-dimethylamino-methylenamino-2, 4, 6-tri-iodophenyl) propionic acid with an iodine content of 61.4 per cent.

One hundred patients were examined with the following technique: On the day before the examination, after the usual preparation, a scout roentgenogram is taken, then 6 tablets of biloptin, 3 gm. active ingredient, are given at 8 p.m., followed by 6 tablets

at 6 a.m. on the day of the examination. Three to four hours after the second dose of the tablets the second roentgenogram is taken to show the hepatic ducts, the common duct, and the gallbladder. The third roentgenogram is taken after cholecystokinin is given.

Forty-five of the 100 patients thus examined were re-examined with biligrafin forte without any observed sensitivities to either drug. The large bile ducts were visualized on the second roentgenogram in 54 cases after the double dose of biloptin. In 62 cases the gallbladder was adequately visualized. In 16 cases visualization was not accomplished with either biligrafin or biloptin. In 80 per cent of the cases in which visualization was not accomplished with biligrafin an adequate gallbladder shadow was noted after the administration of biloptin.

—George Bonk, M.D.

Radiomanometric Exploration of the Biliary Tract (La radiomanometrie biliaire). G. ESPOSITO, R. MATHIS, and R. SOUPAULT. *Cardarelli*, 1960, 2: 23.

WITH THE TERM "radiomanometrie," the French authors indicate the simultaneous cholangiography and manometric measurement of the biliary tract during operation. This examination can be performed with several technical variations, but all the methods are based upon the same general principle.

In this report the technique of Corelli, as used at the Saint Antoine Hospital in Paris, France is described in detail. The examination is performed by means of the apparatus of Foures, which is a pressure-injector completely autoclavable. The fluid injected for pressure measurement is the contrast medium itself, so that the roentgenologic and manometric exploration of the biliary tract can be carried out simultaneously. The contrast medium can be injected into the gallbladder, the common bile duct, or, more commonly, the cystic duct. Rarely can the liver be used as the site of the injection.

This technique, which is used routinely by the authors, is recommended as a safe and convenient method to provide complete, functional, and anatomic exploration of the biliary tract.

—Riccardo Benvenuto, M.D.

Demonstration of Lymph Node Metastases by Pelvic Venography. ERIK CARLSSON, SUMNER HOLTZ, and ALFRED I. SHERMAN. *Am. J. Roentg.*, 1961, 85: 21.

INVOLVEMENT of pelvic lymph nodes by metastatic carcinoma from the cervix has significant bearing on prognosis. Since pelvic irradiation can destroy tumor in pelvic lymph nodes but since, in the dosage required, there is definite hazard of postirradiation complication, it would be of considerable importance to the patient to determine the presence or absence of such metastasis before planning radiation treatment fields and dose. Furthermore the recognition of involved para-aortic nodes would eliminate needless laparotomies, since such involvement makes these patients incurable.

The main groups of lymph nodes affected by metastatic carcinoma from the cervix lie along the vascular channels of the pelvis, and enlarged firm nodes distort the thin walled, low pressure veins. These veins can be opacified by several methods: (1) Pelvic interosseous injection; (2) injection into the dorsal vein of the clitoris; (3) interstitial injection into the uterus; and (4) injection into the femoral vein.

The simplest and safest technique, injection into the femoral vein, has been employed by the authors in 31 cases. Polyethylene catheters are passed over guide wires inserted through percutaneous punctures in femoral veins to a point in the external iliac veins about 10 cm. distal to the bifurcation of the common iliac vein. Twenty-five cubic centimeters of 25 per cent hypaque was injected simultaneously into both catheters, and serial roentgenograms were taken immediately. The examination is made in 2 stages, first without compression of the inferior vena cava and then with compression. Excretory urograms are made at the completion of the examination. There were no serious complications in this series.

Metastatic nodes are manifested by abnormal indentations of veins, nonfilling of part of a vein, displacement of a vein, or demonstration of abnormal anastomoses.

In a series of 23 proved cases with normal venograms, 13 patients had no gross microscopic tumor and 1 showed a microscopic focus in a node. In 9 proved cases with abnormal venograms, 7 patients had gross and microscopic disease. The other 2 had been irradiated after the venography and prior to the laparotomy and showed only enlarged nodes with postirradiation changes.

—Lois Cowan Collins, M.D.

Pelvic Arteriography in Obstetrics. G. I. SOLISH, J. G. MASTERSON, and L. M. HELLMAN. *Am. J. Obst. Gyn.*, 1961, 81: 57.

AFTER THE PRESENTATION of a concise summary of the history of arteriography, the authors describe a method of pelvic arteriography by percutaneous countercurrent femoral injections. Twenty women in various stages of pregnancy were subjected to the procedure and no complications of note were encountered. Radiation exposure was not thought to be a significant problem. Arteriography was demonstrated to be of some value in localization of the placenta in both ultrauterine and extrauterine pregnancies and can be used to distinguish between the two. Certain contributions to basic understanding of placental and uterine circulation can, no doubt, be accumulated by this methodology. The authors did not propose arteriography as a routine procedure but suggested that in certain difficult diagnostic problems the procedure might be of considerable help.

—T. W. McElin, M.D.

RADIOACTIVE ISOTOPES

Radioactive Iodine in the Treatment of Hyperthyroidism. ROBERT VOLPE, DOUGLAS L. SCHATZ, AILEEN SCOTT, JOSEPH A. PELLER, and Others. *Canad. M. Ass. J.*, 1961, 84: 84.

THE ARTICLE deals with the possible biologic hazards from radioactive iodine therapy. Because of the fact that radiation at any level cannot be considered harmless and because of the controversial nature of the subject, the authors have attempted to review

and summarize their viewpoint as to the possible ill effects and hazards implicit in the therapeutic use of radioactive iodine in the treatment of patients with hyperthyroidism.

A review of 542 hyperthyroid patients treated by I^{131} at the Toronto General Hospital, Toronto, Canada between 1950 and 1958 is presented. This group included 403 patients with diffuse hyperplastic goiter and 139 patients with toxic nodular goiter. The authors treat all nonpregnant hyperthyroid patients over the age of 25 years with this isotope. In general, patients with toxic nodular goiters received the larger doses of the drug. Of the group with diffuse hyperplastic disease, 72 per cent were cured with 1 dose, the remainder requiring 2 or more doses. Permanent hypothyroidism was produced in 16.3 per cent of those treated and no late recurrences of hyperthyroidism were noted. Twenty-one deaths occurred within 2 years of therapy but in most there was no obvious relation to therapy and in none was there a clear cut cause and effect relation to I^{131} therapy. Nevertheless, the authors caution that the elderly or very ill patients should be treated only after they have been rendered euthyroid by antithyroid drugs.

Fertility has not been affected by I^{131} therapy, but the use of this isotope in pregnancy is contraindicated because of the possible ill effects. The fear of carcinoma of the thyroid, likewise, appears to be unwarranted if the therapy is utilized only in adults. Leukemia has been reported in 14 instances in the literature. The authors recognize that there may be a slight increase in the incidence of leukemia after treatment with radioactive drugs as compared with that possibly induced by certain diagnostic roentgenologic procedures, but this increase is insufficient to warrant any change in their policy regarding the use of I^{131}.

After consideration of these hypothetical dangers, it is concluded that the use of radioactive iodine is a safe, effective form of therapy for adult, nonpregnant hyperthyroid patients and is to be preferred to surgical thyroidectomy. —*Gordon F. Madding, M.D.*

SURGICAL TOPICS OF GENERAL INTEREST

ETIOLOGIC AND PHYSIOLOGIC RESEARCH

Influence of Unilateral Hypoxia on Blood Flow Through the Lungs in Man in Lateral Position. M. Arborelius, Jr., G. Lundin, L. Svanberg, and J. G. Defares. *J. Appl. Physiol.*, 1960, 15: 595.

Hypoxia in one lung causes a shift of blood flow to the other lung in normal supine subjects. This shift is not accompanied by any changes in the relative ventilation of the lungs. The combined effects of lateral position and hypoxia of the lower lung on pulmonary circulation have been studied.

The hypoxic stimulus does not overcome the gravitational factor that normally shifts the blood from the upper to the lower lung in the lateral position. Only in the absence of the gravitational factor does the unilateral hypoxia exert its shifting action uniformly in all normal subjects studied. The term gravitational factor is, of course, used only pictorially and does not imply a real understanding of the process. In other words, the hypoxia does not overcome the hydrostatic and other factors which normally shift the blood from the upper to the lower lung in the lateral position. Hypoxia is thus a weaker stimulus and seems to exert measurable influence on blood distribution only between parts of the lung in which the hydrostatic and dynamic factors are of the same magnitude.

—*Harold M. Unger, M.D.*

Modification of the Radiation Effect on Tumors by Cortisone in Intact and Adrenalectomized Animals. Henry P. Plenk and Roger B. Fuson. *Cancer*, 1960, 13: 1188.

After the anterior chamber transplantation of 2 mammary carcinomas and 1 neuroblastoma into susceptible strains of intact mice, irradiation of 3,000 r to the orbit on the fourth posttransplant day resulted in 45 per cent survivals at the end of 70 days.

The administration of cortisone plus roentgenotherapy increased the percentage of survivals to 71 per cent.

Of the adrenalectomized animals receiving therapeutic doses of cortisone plus roentgenotherapy, 59 per cent survived 70 days compared to 43 per cent of the animals that received only a maintenance dose of cortisone plus roentgenotherapy.

The cortisone effect was apparent when the hormone was given at the time of irradiation. Prolonged administration did not increase the percentage of survivors.

A dose of 0.05 mgm. of cortisone, 2.5 times the maintenance dose, was at least as effective as were larger doses as expressed in the number of mice surviving 70 days.

The synergistic cancerocidal effect of cortisone and irradiation is assumed to be due to a modification of the radiation sensitivity of the tumor and not due to a direct effect of cortisone on tumor growth per se.

The authors find no evidence to suggest that the simultaneous administration of cortisone and roentgenotherapy has any harmful effects. If animal experiments could be applied to man, the combined effect might prove to be beneficial in increasing the radiation response of some tumors.

—*John J. Maloney, M.D.*

Experimental Production of Acute Renal Tubular Necrosis. Martin S. Litwin, Carl W. Walter, and Neil Jackson. *Ann. Surg.*, 1960, 152: 1010.

In investigating the cause of acute renal tubular necrosis, the authors have previously demonstrated the following three variables in the experimental production of this lesion: (1) The degree of renal ischemia; (2) the excretory state of the kidney at the noxious moment; and (3) the quantity of heme pigment circulating in the blood.

The first experiment performed in the present report is designed to study a fourth variable; the presence of gram-negative bacteria after severe soft tissue trauma. A carefully controlled group of 30 dogs was utilized. Six of the animals were subjected to tourniquet trauma of a hind limb, 10 were subjected to sublethal doses of gram-negative bacteria, and 14 were subjected to both of these insults. Hypotension was treated with intravenous plasma expanders in all groups.

Renal tubular degeneration occurred only in the group suffering both tourniquet trauma and gram-negative bacterial injection. This group was further divided into 2 groups; 10 of the animals received 5 ml. of bacterial suspension containing 5×10^8 Escherichia freundii and the remaining 4 received 0.25 ml. containing 2.5×10^7 Escherichia freundii. None of the latter group had tubular degeneration, whereas all of the former group did. Acid hematin was demonstrated in the urine of animals in which tubular degeneration developed. The toxicity of sterile aqueous solution of acid hematin was demonstrated in mice and dogs. The formation of toxic acid hematin by acidification of hemoglobin and myohemoglobin in glomerular filtrate is thought by the authors to be a possible cause of acute tubular degeneration in their experimental animals.

In order to test the hypothesis arrived at in the first experiment, a second set of experiments was utilized. Acid hematin in moderate doses alone, 1.5 gm./kgm., did not cause tubular degeneration in any of 4 animals. Previous work by the authors had demonstrated that ischemia due to renal artery occlusion for 30 minutes resulted in no changes in renal function. It was found in these experiments, however, that moderate doses of acid hematin together with either renal ischemia, dehydration by water deprivation for 3 days, or renal vasoconstriction by simultaneous pitressin administration did result in renal tubular degeneration by both histologic and physiologic criteria. These results again lead the authors to postulate that acid hematin is the etiologic agent in the production of renal tubular necrosis after hemoglobinemia.

—*C. Thomas Fitts, M.D.*

Examination of Joint Effusion by Means of Electrophoresis (Die Bedeutung der Elektrophorese bei der Untersuchung von Gelenkerguessen). KARL VIERNSTEIN. *Zschr. Orthop.*, 1960, 93: 531.

ELECTRIC MOBILITY of proteins can be measured by either the Tiselius apparatus or saturated filter paper. A comparison of the results obtained by these two methods showed insignificant differences. The results of examinations of normal joint fluids and joint fluids in acute, serous effusions found in meniscus injuries and dislocations of the knee joint were discussed. Effusions in arthrosis deformans, chronic and serous effusions found in chronic meniscus injuries and free joint bodies and in conditions with degenerative changes of the articulating cartilage were also analyzed. Exudates in joints of patients with infectious arthritis, polyarthritis, and tuberculous arthritis were also evaluated.

Fractions of protein were evaluated and compared and the relationship of the alpha 1, alpha 2, and beta globulin and albumin ratios were established. Under normal circumstances the ratio of beta globulin to gamma globulin usually is 8.7 to 1, in acute serous effusions the ratio was 5 to 1, in chronic serous effusions it was 3.4 to 1, in degenerative changes, 3.4 to 1, and in infectious arthritis, 1.6 to 1.

In mild cases of arthritic joint effusions, the albumin to globulin ratio was nearly the same as in blood serum. In severe cases, however, an increase of the globulin values was found in the joint effusions. In cases of inflammatory exudates, the globulin values were greatly increased while the albumin values were significantly lowered. Similar changes in globulin and albumin values were also observed in the serum of patients suffering from these conditions, which would indicate that the changes in the albumin to globulin values in the joint itself were not caused by any significant change of the functions of the synovial membrane but are part of a change in the general condition of the patient.

Ordinarily the endothelial cells and membrane of the capillaries are not permeable to colloids. This is not true of the capillaries of the synovial membrane, as colloids pass freely through the capillary endothelium. Any irritation of the synovial membrane is characterized by increased permeability to globulin. The amount of globulin found in joint effusions can be directly correlated to severity of the effusion. In chronic irritative conditions and chronic arthritic conditions of the knee joint the albumin to globulin ratio found in the joint fluid is very similar to the values found in the blood serum of the patient. Only in traumatic joint effusions is the albumin to globulin ratio equal in the joint fluid and in the serum.

—*George I. Reiss, M.D.*

CANCER RESEARCH AND CHEMOTHERAPY

Evaluation of Annual Examinations in the Detection of Cancer. CONRAD B. JENSON, DONALD B. SHAHON, and OWEN H. WANGENSTEEN. *J. Am. M. Ass.*, 1960, 174: 1783.

THE STATISTICS from the Cancer Detection Center of the University of Minnesota in Minneapolis suggest that yearly examinations bring about earlier detection of cancer and improved prognosis. The examinations were limited to asymptomatic residents of Minnesota over 45 years old if female; over 50 years old if male. The examination included gastric analysis, proctosigmoidoscopy, pelvic examination, complete blood count, urinalysis, and roentgenogram of the chest. Roentgenographic examination of the upper gastrointestinal tract and colon were performed if indicated. Patients were urged to return annually for re-examination.

In the past 11 years and 2 months there were 33,224 examinations of 9,123 patients. As a direct result of these examinations there were found 163 cases of cancer of the breast, stomach, large intestine, prostate, ovary, or uterus. Cancers which were identified by other physicians in the intervals between annual examinations at the clinic are not included in this study.

The cancers discovered on subsequent annual examinations were compared with those found on initial examination. It was found that there was less lymph node metastasis associated with the tumors discovered on subsequent examinations and that results of treatment were better in this same group. It appears also that the results of treatment of all the asymptomatic patients in both groups are better than those usually reported in statistics of cancer treatment, thus emphasizing the effectiveness of this type of program. —*Lockert B. Mason, M.D.*

Immunological Differences Between Normal and Malignant Cells. R. C. NAIRN, H. G. RICHMOND, M. G. MCENTEGART, and J. E. FOTHERGILL. *Brit. M. J.*, 1960, 2: 1335.

AN ALTERATION in cell constituents associated with malignant change was investigated by immunologic methods at the University of Aberdeen, Aberdeen, Scotland. Three types of normal tissue and three of tumor tissue were compared: rat liver and hepatoma; hamster kidney and renal carcinoma; and human skin and various skin tumors. In each study antigen was prepared from homogenized normal tissue, which was centrifuged to remove tissue fragments and cell nuclei. For the three studies rabbits were immunized with supernatants.

With the use of appropriate tissue preparations to absorb and remove nonorgan-specific antibodies, the rabbit antisera were tested against the corresponding normal and tumor tissues by three methods: (1) complement fixation; (2) gel-diffusion; and (3) fluorescent staining. Control studies were carried out with normal serum and immune serum specifically neutralized by absorption with preparations of the homologous organ. In the experiments with rat liver and hamster kidney all three methods indicated the presence of an organ-specific antigen in liver and kidney; the antigens were either absent from, or at most present in very small amounts in, the corresponding tumor tissue. In the malignant tumors of the skin a partial depletion of specific antigen was demonstrated. The fluorescent-antibody studies suggested that the specific antigen is localized in the cell membrane and in the perinuclear zone.

One interpretation of these findings is that an organ-specific antigen which is a growth-controlling factor may be lacking in malignant cells. The locali-

zation of the antigen to normal cell membrane may have special significance and may be related to surface identification of the cell. Controlled normal growth may require such a self-regulator, and its absence might lead to uncontrolled malignant growth.

—*Stephen W. Carveth, M.D.*

The Trials in the Cytological Diagnosis of Gastric Cancer. YOSHIYUKI YOSHIDA. *Arch. jap. Chir.*, 1961, 30: 36.

THE AUTHOR DESCRIBES an abrasive balloon device for use in the cytologic diagnosis of gastric cancer. The apparatus consists of a single lumen polyvinyl tube 100 cm. long covered by a sheath. Two balloons are kept in the distal portion of the sheath while the tube is being passed. The distal balloon is smaller and is devised for obtaining cells from the antrum. The larger proximal balloon is for obtaining cells from the corpus and cardiac portions of the stomach. They can be protruded from the sheath by a wire cable.

The gastric cytologic findings in 139 patients were studied, and results are reported on 119 patients in whom confirmation of diagnosis was available. The present technique, using a sheath to pass and withdraw the abrasive balloons, prevents the pickup of many cells exfoliated from the oroesophageal tract, which may be confusing. The loss of the specimen en route in the oroesophageal tract is prevented. The distal abrasive balloon reaches the antrum and pyloric region. The accuracy of diagnosis of gastric cancer by this method appears better than by previous cytologic techniques. —*Lloyd D. MacLean, M.D.*

Gastrocytogram, a New Histochemical Technique for the Differentiation of Cells in the Gastric Sediment (Gastrocitogramma; applicazioni di un metodo istochimico nella differenziazione delle cellule del sedimento gastrico). G. TIRELLI. *Arch. ital. mal. app. diger.*, 1960, 27: 330.

THE CYTOLOGIC INTERPRETATION of gastric sediments offers a formidable challenge even to the experienced pathologist. In order to simplify this test, which proved to be very useful in the diagnosis of several diseases of the stomach, a new method of staining for the gastric cells present in the sediment has been developed at the University of Genoa Medical School, Genoa, Italy.

This article is simply a preliminary report describing the technical details of the method. A critical evaluation of the technique, as compared to the standard methods, is also given. The method is based upon the use of histochemical staining techniques, specific for the mucopolysaccharides. This procedure makes differentiation of the cellular elements easier and consequently interpretation of the findings easier.

In a series of 30 patients not suffering from gastric diseases, gastric lavages were performed. The cells present in the sediments were stained with the conventional techniques and with the method under discussion and the results compared. The results were almost identical and this is regarded by the author as proof of the reliability of his method. The results obtained in the diagnosis of nonneoplastic diseases of the stomach will be reported in further articles.

—*Riccardo Benvenuto, M.D.*

Induction of Neoplasms in the Thyroid Gland of the Rat by X-Irradiation of the Gland. S. LINDSAY, G. E. SHELINE, G. D. POTTER, and I. L. CHAIKOFF. *Cancer Res.*, 1961, 21: 9.

IRRADIATION has been implicated in the development of benign and malignant thyroid neoplasms in both the rat and the human being. In this article the authors describe an experiment with 450 rats 8 to 12 weeks of age. They were divided into 5 groups and various doses of roentgen irradiation were applied to either the entire thyroid gland or to one lobe of the thyroid gland. A suitable number of controls received no irradiation. A description, both gross and microscopic of the thyroid parenchyma, thyroid neoplasms, parathyroid lesions, and other neoplasms follows in this article which is profusely illustrated with photomicrographs.

One hundred and seven rats survived for 2 years after the thyroid irradiation. These rats were anesthetized and exsanguinated and complete autopsies were performed.

Grossly the irradiated glands were, as a rule, smaller than those of control animals and the decrease in size was proportional to the dose of roentgen rays administered. The pathologic lesions observed in the parenchyma of rat thyroid glands irradiated with roentgen rays closely resembled those observed previously in rat thyroids internally irradiated with I^{131} and those found in human thyroid glands subjected to various forms of irradiation. The severity of the lesions in the rat thyroid glands was proportional to the dose of irradiation administered. Mitotic figures were absent from the glands that showed radiation injury, indicating a depressed capacity of the externally irradiated gland to respond in a normal fashion to thyrotropic hormone.

Benign nodules or adenomas were observed in 30 of the 74 irradiated rats that survived. These lesions appeared to have originated as foci of nodular regeneration and hyperplasia. Thyroid adenomas were noted in 3 per cent of the controls and in 18 to 75 per cent of the irradiated animals. Papillary carcinomas and follicular carcinomas were not seen in the control animals but were found in 9 of the irradiated rats. Two of the 6 papillary carcinomas appeared to have originated in previously benign adenomas. Naturally occurring alveolar or lobular carcinomas had an incidence of 33 per cent in normal control rats and of 22 to 45 per cent in rats whose thyroids were irradiated with roentgen rays. These naturally occurring carcinomas were of low grade malignancy and were unlike those induced by irradiation. Parathyroid hyperplasia and adenomas were observed in control as well as in irradiated rats. Other neoplasms were found in both control and irradiated rats and only 1, an epidermoid carcinoma of the trachea, was thought to be due to irradiation. —*Donald M. Clough, M.D.*

Effect of Repeated Surgical Wounding on the Growth Rate of a Tumor Graft. BERNARD GOTTFRIED, NORMAN MOLOMUT, and LUDMILA SKAREDOFF. *Ann. Surg.*, 1961, 153: 138.

CLINICAL EXPERIENCE has shown that tumor growth is often accelerated after operative trauma. It has been shown that animals subjected to celiotomy show in-

creased pulmonary metastases from intravenously inoculated cancer cells. This article reports the influence of surgical trauma on experimental tumor growth.

Surgical wounds are made in the nuchal area of normal adult C3H mice. These wounds are kept open and clean during the test period. In the test group of mice fragments of mammary adenocarcinoma H 2712 are placed adjacent to the surgical wound, whereas in the control group of mice tumors are similarly placed in the absence of a surgical wound.

The presence of the wound resulted in significantly more animals with larger tumors than among the control mice. The tumors in the wounded mice appeared earlier and grew faster than in the control mice. These data give experimental evidence supporting the surgeon's clinical observations of accelerated tumor growth after trauma.

Previous studies have shown humoral factors in injured tissue which may stimulate growth in normal wound healing. Cells subjected to injury release proliferation-promoting substances thought to be hormone-like substances secreted by living injured cells rather than solely the products of cell destruction. The exact role of these factors is the subject of current investigation.

A biochemical lesion in the repair process may be a forerunner of a neoplastic change. The authors are currently attempting to isolate and characterize the mechanism and components which stimulate the regeneration of injured cells and determine the direct influence on cancer cells. —*Patrick F. Jewell, M.D.*

Effects of a Single Pituitary Isograft on Mammary Tumorigenesis in Mice. ANNABEL G. LIEBELT and ROBERT A. LIEBELT. *Cancer Res.*, 1961, 21: 86.

SINGLE PITUITARY ISOGRAFTS were transplanted either subcutaneously or intraocularly into female mice lacking the mammary tumor agent, DBA/2/f and (C57BL X DBA/2/f) F_1 hybrids, as well as into mice with the mammary tumor agent, RIII and (RIII X C57BL) hybrids. All animals bearing a viable graft showed stimulated mammary glands with mild secretion and functioning corpora lutea. Such animals were capable of breeding and nursing their young.

Mammary cancers developed in the agent-free DBA/2/f and (C57BL X DBA/2/f) F_1 hybrid mice with pituitary grafts. Pregnancy and lactation influenced mammary tumorigenesis in control RIII mice, but the milk secretion induced by a pituitary graft had a variable effect on tumorigenesis. Mammary cancer developed in force-bred RIII females bearing a pituitary isograft at the same time as in force-bred controls, suggesting a maximum threshold for hormonal stimulation in mammary tumorigenesis.

RIII mice with grafts and allowed to nurse showed a later mean survival than did nongrafted mice. The C57B1 strain contributes some form of "genetic resistance" to the (RIII X C57BL) F_1 hybrid as manifested by a delay in tumor appearance as compared with that in the force-bred RIII parent stock. This delay in time of tumor appearance was overcome by the effects of a pituitary isograft. The pituitary isografts in all strains showed an increase in size with time, whether transplantation was subcutaneous or intraocular, and appeared histologically similar to chromophobe adenomas.

The results of this study indicate that a single pituitary isograft removed from its hypothalamic influences can have significant effects on the development of mammary cancers in intact mice depending upon genetic factors, the presence or absence of the mammary tumor agent, and the breeding history.

—*Ernest D. Bloomenthal, M.D.*

Mechanism of Mammary Duct Stimulation by Tumor Transplants. BERTIE F. ARGYRIS and THOMAS S. ARGYRIS. *Cancer Res.*, 1961, 21: 75.

SUBCUTANEOUS epithelial Ehrlich ascites tumor(EAT) transplants stimulate adjacent mammary duct epithelium in C57BL mice. Present data describe a similar effect for sarcoma 180, which is of connective tissue origin. Increased mitotic activity, with peak value on the second day of tumor growth, occurred in the epithelial cells of mammary ducts located in a 1 mm. area around the tumor nodule. Inward proliferation and enlargement of mammary duct cells resulted in increased height of epithelial lining and obliteration of the duct lumen.

The role of individual tumor components, namely, the ascitic fluid, the tumor cells, and the necrotic and connective tissue, was determined. Ascitic fluid, devoid of tumor cells, had no effect on mammary duct epithelium. Nor was ascitic fluid required for growth of EAT cells, since saline-washed cells grew as usual and stimulated adjacent mammary duct epithelium. In vitro irradiation of tumor cells, which inhibited cell multiplication but not cell metabolism, decreased but did not eliminate the capacity of tumor cells to stimulate mammary duct cells.

Implants of necrotic tissue did not affect adjacent mammary ducts significantly; nor did the connective tissue capsule, which surrounded transplants of boiled tumor cells, have any significant effect on adjacent mammary duct epithelium. Severe connective tissue proliferation and damage, as induced by paraffin pellets, did, however, produce a high mitotic activity in mammary duct cells, but only in those ducts which were in direct contact with the area of damage. Failure of EAT cells growing in the vaginal wall of ovariectomized mice to induce cornification of the overlying vaginal epithelium suggested that mammary duct stimulation by tumor transplants was not due to a local secretion of estrogen by the tumor cells.

These results suggested that living but not necessarily dividing tumor cells were required for mammary duct stimulation. —*Ernest D. Bloomenthal, M.D.*

Ultrashort Wave Irradiation of Pituitary for Cancer Control (Versuche zur Beeinflussung maligner Tumor en beim Menschen). ERWIN SCHLIEPHAKE. *Münch. med. Wschr.*, 1960, 102: 2020.

THE AUTHOR has treated 80 patients with advanced cancers, many of them recurrences after operation or roentgen radiation, with short wave radiation to the hypophysis and diencephalon. He uses glass plate electrodes with an air distance of 4 cm. to forehead and occiput, with the patient sitting up and awake. The first treatment lasts 8 minutes, increased daily up to 12 to 15 minutes. Then the treatments are given

every other day for awhile and then 3 times per week.

The patients had brain tumors and stomach, bowel, lung, and breast carcinomas with metastases. Twenty of the 80 patients were definitely improved, a few even free of symptoms. Many improved for a while and then died of their disease. A histologic diagnosis was obtained in most but not all of the patients—some diagnoses were established by roentgenographic findings alone. Some patients improved and then did not return.

There is usually no sign of improvement for the first 3 to 4 months of these treatments. As yet, there is no exact dosage schedule. The treatments are not unpleasant; the patients feel a slight sensation of warmth in the head and occasionally dizziness. If, at the end of 4 months, the patient's condition is worse, further treatments will probably be useless. If, however, there has been improvement, treatments are continued. Several patients have been treated for 7 years, and 1 for 25 years.

The author presents the cases of 15 patients who reacted favorably. He admits that statistical evaluation of the series is difficult. The successfully handled patients did not have merely a few extra months of tortured existence, however. They gained weight, were relieved of pain, and some went back to work. With better follow-up studies perhaps there could have been more successes, but some patients who came from a distance felt better and did not return. The author lists as successes only those whom he still sees in follow-up and is still treating. The longest interval between treatments is 2 weeks. He found that most of the patients who ceased receiving treatments had relapses in 3 to 4 months.

A disadvantage to the method is the necessity for indefinitely prolonged treatments. However they are simple and not injurious, and the method shows enough promise to be added to other presently available therapeutic measures for advanced cancer.

—William B. Gallagher, M.D.

Host-Tumor Antagonism—XVII, Trauma and Cancer. LOUIS PELNER. *J. Am. Geriat. Soc.*, 1961, 9: 58.

THE AUTHOR gives a detailed review of the subject of posttraumatic cancer. There are three possible mechanisms relating cancer to trauma: (1) cell mutation may occur as a result of the local environmental change accompanying the process of repair after injury; (2) trauma may act as a cocarcinogen; and (3) a carcinogenic agent may accompany the agent inflicting the injury.

From the case reports, pertinent experimental evidence, and data in discussions it appears that cancer in man can result from a single trauma, although this must be considered a rare occurrence. Therefore, trauma is neither the most important nor the most frequent cause of cancer. Sarcoma is the type of cancer most often found to be associated with trauma.

The concept that a single trauma may activate a latent cancer cell may explain some of the recorded cases. The effect of a single trauma on the stimulatory and inhibitory factors in the cellular environment is also important and may determine whether or not a cancer results.

In a number of cases, trauma only calls attention to a pre-existing unrecognized cancer.

There is no evidence that single trauma is a significant factor in the cause of tumors of the internal organs.

—David E. Hallstrand, M.D.

Turnover of Plasma Iron in Cancer Patients Prior to and After Treatment. G.-C. HEVESY and H.-L. KOTTMEIER. *Acta obst. gyn. scand.*, 1960, 39: 675.

A SHORTENED LIFE SPAN for erythrocytes and an increased iron turnover in patients with cancer have been reported by other investigators. The present study was undertaken to determine how these factors in patients with carcinoma of the uterine cervix are affected by irradiation therapy.

The mean life span of the erythrocytes in these patients was found to be 20 per cent shorter than that of the healthy controls. Although in some cases there was an increase to normal, the mean life span of the red blood cells for all the patients did not change significantly after successful irradiation therapy.

Plasma iron turnover was determined with radioactive ferric chloride ($Fe^{59}C_3$), and the individual hematocrit values were used to calculate the results in order to eliminate discrepancy due to possible error in plasma volume and to allow the results to be expressed in milligrams of iron turnover an hour per liter of red blood cells (l. RBC). By this method the turnover in 5 patients with benign pelvic disease averaged the normal figure, 0.76 mgm./hr./l.RBC.

Plasma iron turnover was increased in all 23 cases of invasive carcinoma, the values ranging between 0.77 and 1.82 mgm./hr./l.RBC, the mean value being 1.22 mgm./hr./l.RBC. One year after irradiation, the test was repeated. The individual values were reduced in 16 of 18 patients treated successfully, and the mean value was 0.75 mgm./hr./l.RBC, a significant difference (p 0.001). It was also noted that the hemoglobins were increased and the plasma volumes reduced. In the 5 cases with recurrence the plasma iron turnover remained elevated. Three of these patients showed an increase several weeks before clinical recurrence was evident, and in 1 this led to early laparotomy and removal of a carcinomatous mass.

Three of the 4 patients with carcinoma in situ had elevated plasma iron turnover. All were treated with cold knife conization and on follow-up of 2 of them, 1 of whom received irradiation as well, the values were reduced to normal. *—James J. Mongé, M.D.*

Cancer Cells in the Circulating Blood During Operative Management of Genitourinary Tumors. OLGA JONASSON, LEROY LONG, STUART ROBERTS, ELIZABETH MCGREW, and JAMES H. MCDONALD. *J. Urol.*, Balt., 1961, 85: 1.

THE DEVELOPMENT of hematogenous metastases after operation or manipulation has long intrigued the surgeon. Although most malignant tumors are usually considered to spread via the lymphatics, tumors of the urinary tract have been shown to have a significant incidence of blood-borne metastasis.

The authors present a careful study comparing the presence of carcinoma cells in the blood stream during and after manipulation. One hundred and three patients with various genitourinary tract diseases were

studied. The 90 malignant lesions were divided roughly into curable and incurable. Cancer cells were present in the blood of 11 of the 35 of the curable patients and of 24 of the 55 incurable patients. Of the 13 patients with benign lesions, no malignant cells were found in the blood. Soap and water washing of the skin in preparation for kidney operation increased the number of cells markedly. Bimanual examination caused more liberation of cells apparently than does a transurethral resection.

The manner of spreading malignant cells or the alternate fate of the disseminated cancer cells has not been illustrated, but it is generally considered that the more circulating neoplasm, the more chance there is of metastatic carcinoma.

Gentleness of approach at all manipulative procedures involving the genitourinary tract and ligation of the venous drainage at the earliest possible opportunity are stressed and readvised.

This article serves to reaffirm the carefully taught principles that tissues should be handled gently and that any vessels that may give egress should be blocked early in the operative procedure. This teaching is nothing startling or new, but is important and bears repetition. The interesting part of this article is that the authors prove an old theory.

—John R. Herman, M.D.

Prevention of Implantation of Cancer Cells in the Wound by Irrigation with Anticancer Agents. G. O. McDonald, J. L. Edmondson, and W. H. Cole. *Am. J. Surg.*, 1961, 100: 16.

Surgeons have known for years that cancer cells might be implanted in a wound during operation for malignant disease, thereby causing local metastases. Inadequate attention has been given this problem, however. Various writers have reported such local recurrences after operations on the neck, radical mastectomy, perineal excision of the rectum, and bowel resections. It has been shown experimentally that a suture passed through a cancer will transplant tumor cells along the needle tract. The highest percentage of local recurrences are reported in neck wounds after radical resections for cancer. These recurrence rates vary from 20 to 40 per cent. Among patients with radical mastectomy, recurrences of 10 to 15 per cent are reported, whereas this rate is only 7.5 per cent in patients who had no biopsy before radical mastectomy.

Experiments were devised to test agents which might aid in preventing this local contamination by tumor cells. Walker 256 carcinosarcoma from female albino rats was removed, minced, and suspended in saline. A concentration of 20,000 unstained, viable cells per c.c. was obtained. A subcutaneous pouch was created on the ventral surface of the rat and 0.5 c.c. of tumor suspension was placed in this pouch. After an hour, the pouch was opened and irrigated for 35 seconds. Twenty-five chemicals or solutions were used for irrigation. Various concentrations of some agents, e.g., clorpactin, formaldehyde, styrlquinoline, and others were used to determine what the tissues might tolerate. Clorpactin, for example, is an effective anticancer drug in 2 per cent solution but in this strength is not clinically tolerated. The most effective agents were nitrogen mustard in a concentration of 1 or 2 mgm. per cent and sodium hypochlorite, Dakin's solution 0.5 per cent buffered to pH 9.0. Since nitrogen mustard would not be used in the wound if it was also to be given systemically, the authors chose sodium hypochlorite for clinical trial. This solution must be freshly prepared just before use; otherwise it deteriorates and becomes toxic.

The procedure for preparing sodium hypochlorite solution for clinical use is described. Although frequent wound irrigations during long operations might be desirable, the authors consider it adequate to irrigate at the end of the operation. The wound is flooded for a minimum of 4 minutes. Pleural and peritoneal cavities are similarly irrigated if these have been entered. After irrigation, the fluid is aspirated, although there is no evidence that a small amount of remaining solution would be harmful. New wound drapes, gowns, gloves, and instruments are used for the closure. This technique is now undergoing further clinical evaluation. *—Emile L. Meine, Jr., M.D.*

The Fate of Circulating Tumor Cells—I, Passage of Cells Through Capillaries. Irving Zeidman. *Cancer Res.*, 1961, 21: 38.

Circulating tumor cells begin the formation of a metastasis when the tumor cell embolus lodges in a small vessel of a distant organ. In a series of experiments microcinematic studies were made of the arterocapillary junctions of the mesentery of domestic rabbits while suspensions of tumor cells were injected into the mesenteric artery simultaneously. The transplantable V2 carcinoma and Brown-Pearce carcinoma were utilized. Many photographs show the actual passage of the tumor cells through small capillaries, frequently in cases in which the cell was considerably larger than the lumen of the vessel.

Many of the Brown-Pearce cells were very large but they were seen to be remarkably plastic and, upon engagement in the capillary tube, considerable distortion of the cell occurred, allowing it to pass through the vessel. Many of the V2 carcinoma cells revealed a similar ability to distort to fit the lumen, but some of the V2 cells appeared more rigid and were permanently arrested either at the arterocapillary junction or in a nearby segment of the capillary. All the rabbits were sacrificed 1 month after injection and the intestinal loops were examined. Tumor was found in over 95 per cent of the animals, often in the form of miliary mesenteric nodules distal to the site of the injected mesenteric artery.

The author concludes that tumor cells can distort to fit the narrow capillary tube and still pass through the capillary circulation into the veins. An occasional cell appears too rigid to fit into the capillary tube and is thus arrested. The incidence of permanent cell arrest varies with the type of tumor.

—Wayne F. Cameron, M.D.

Use of Cyclophosphamide in Advanced Malignancies. M. Aronovitch, J. F. Meakins, and M. Groszman. *Canad. M. Ass. J.*, 1960, 83: 997.

The authors used cyclophosphamide in treating 43 patients with advanced malignant disease. They believe that this substance is one-third to one-half as

toxic to the ordinary body tissues as is N-oxide-mustard gas. They describe the breakdown of cyclophosphamide as follows: There is a cleavage of the cyclophosphamide connection and cleavage of the phosphamide bridge between the mustard nitrogen atom and the phosphamide ring. This cleavage occurs only in the cell and not in the circulating blood. Because of its infinity for intracellular enzymes, the compound is more easily taken up by some rapidly growing cells and is therefore taken up in greater quantity by the neoplastic cells. As soon as it is formed, it begins to break into the imine linkage which reacts quickly with the enzymes, amino acids, and the desoxyribonucleic acid of the cell nucleus. The authors treated a variety of malignant lesions. Fifteen of the patients had bronchogenic carcinomas and 10 of them showed clinical improvement manifested by relief of pain or cough, and especially of the pain due to metastases. Regression was shown roentgenographically by a decrease in size of the masses in the lung or mediastinum or by disappearance of pleural fluid. When indicated, other forms of therapy were also used including roentgenotherapy. —*Alan Thal, M.D.*

Clinical Trial of the Cytostatic Agent A-139(2,5-Bis [1-Aziridinyl]-3, 6-bis[2-methoxyethoxy]-*p*-benzoquinone). CLYDE O. BRINDLEY, JACOB COLSKY, MARGARIDA M. DEDERICK, JAMES F. HOLLAND, and Others. *Cancer Res.*, 1960, 20: 1580.

CYTOSTATIC AGENT A-139 (2,5-bis [1-aziridinyl]-3, 6-bis [2-methoxyethoxy]-*p*-benzoquinone) was given to a total of 89 patients with cancer in various advanced stages to determine dosage levels and therapeutic effects. Forty-four of the patients had been previously treated with myelosuppressive agents, i.e., alkylating drugs, folic acid antagonists, or irradiation. Palpable tumor masses were measured by caliper weekly, and lesions demonstrated on roentgenograms were measured at 2 to 4 week intervals. Hemopoietic, renal, and hepatic functions were followed up by the usual laboratory methods. The drug was given by the oral as well as the intravenous routes. In this study, A-139 was found to have a toxicity similar to that of the other alkylating agents, namely, hemopoietic depression, gastrointestinal disturbances, local necrosis, and phlebitis at injection sites. The drug has antitumor activity when given by both oral and parenteral routes.

Antitumor effects were seen in lymphoma and in mammary, ovarian, uterine, colon, and bronchiolar adenocarcinoma. The response of 1 patient each with uterine, bronchiolar, and colon cancer is of interest since uterine and gastrointestinal cancers usually do not respond to alkylating agents. Therefore it appears that further study of the effect of A-139 on adenocarcinomas from the lung, uterus, and gastrointestinal tract is indicated. —*John J. Hudock, M.D.*

Nitrogen Mustard and the Steroid Hormones in the Treatment of Inoperable Bronchogenic Carcinoma. JULIUS WOLF, PAUL SPEAR, RAYMOND YESNER, and MARY ELLEN PATNO. *Am. J. Med.*, 1960, 29: 1008.

AMONG the malignant neoplasms for which a chemotherapeutic or a systemic form of treatment is urgently needed is bronchogenic carcinoma. The authors used 5 drugs for their study; nitrogen mustard, diethylstilbestrol, testosterone propionate, progesterone, and cortisone. These agents were compared with a regimen in which the patient received the same intensive supportive care but without any additional specific treatment. It was hoped that from this study an evaluation of these agents as effective means of treating bronchogenic carcinoma could be made.

Four hundred and ninety-six patients with bronchogenic carcinoma were divided into comparable groups and those in each were treated for 3 months with the agents listed. Sixty-three per cent of the patients given nitrogen mustard were alive at the end of 90 days as compared to 51 per cent of the patients receiving the inert compound and 37 per cent of the patients treated with cortisone. The first course of nitrogen mustard improved the survival rate at the thirtieth day only; a second course of the drug failed to exert any further effect on survival.

The median survival time for the control group was 93 days as compared to 121 days for the group receiving nitrogen mustard and 56 days for the patients given cortisone. The results with the other drugs were intermediate between those with the inert compounds and cortisone.

Thirteen patients died of exsanguinating hemorrhage; 6 had received stilbestrol and 5 had keratinizing squamous carcinoma as compared to an over-all incidence of 6 per cent of this type of bronchogenic carcinoma in this series.

—*Gordon F. Madding, M.D.*

Toxic Marrow Failure After Treatment of Carcinoma with Cytotoxic Drugs. IAN CAMPBELL CREE. *Brit. M. J.*, 1960, 2: 1499.

THIS ARTICLE reports the results in 17 patients who were treated for carcinoma of the breast by means of operation and cytotoxic agents. Five of the patients had severe bone marrow depression and form the basis of this report.

The patients were treated with 200 mgm. of testosterone propionate intramuscularly daily, 5 days a week for 5 weeks. In addition they were given thioTEPA, 30 mgm. intramuscularly on alternate days for a total of 9 doses. Two of the patients were treated with another agent, mannomustine, because of the unavailability of thioTEPA.

Toxic damage of the bone marrow was evidenced by a fall in the white blood count to below 3,000/cubic millimeter and a corresponding fall in the platelet count to 100,000/cubic millimeter or less.

It is important that the white cell and platelet counts are repeatedly checked and followed up for a period of weeks after the cessation of therapy. This need is pointed out by the delayed fall of these elements of the blood in 1 of the cases reported. The cases of 2 patients with cytotoxic depression of the bone marrow and their response to therapy are reported in detail. Attention is called to the likelihood of spontaneous recovery. —*John H. Davis, M.D.*

Social Factors in the Epidemiology of Cancer at Various Sites. SAXON GRAHAM. *Ann. N. York Acad. Sc.*, 1960, 84: 795.

THE MOST RELIABLE KNOWLEDGE regarding the cause of scrotal cancer is epidemiologic and involves social

factors in large part, yet it still remains to identify the carcinogen in soot. It is also known that Japanese-Americans have more gastric cancer than others, which suggests an investigation of their diets as compared with the diets of others.

The most well known social factor related to cancer is that of cigarette smoking to cancer of the lung. Recent figures have shown a mortality of 245 per 100,000 from cancer of the lung in cigarette smokers as compared with 33 per 100,000 in nonsmokers.

It has also been known for years that the incidence of cancer of the cervix among Jews is much lower than in nonJews and the relationship to circumcision has been pondered. The lower incidence of cancer of the breast in mothers who have nursed their children is also well known.

A great deal of research is necessary into the social characteristics of each of the groups in which there appears to be a relationship to cancer in order to determine if the social relationship is genuine or spurious. —*David E. Hallstrand, M.D.*

ORGAN TRANSPLANTS

Clinical and Biologic Effects of Heterologous Hypophysial Implants (L'eteroinnesto di ipofisi nei suoi effetti clinici e biologici). G. DELLEPIANE, A. BOCCI, and F. VISCHI. *Min. gin.*, 1960, 12: 814.

THIS STUDY was carried out at the Department of Obstetrics and Gynecology of the University of Turin Medical School, Turin, Italy.

In the period 1952 to 1959, 66 women underwent heterologous hypophysial implants as a treatment for pituitary hypogonadism. In 15 cases an associated hypothalamic dysfunction was also present. An average of 2 or 3 implants were made in each patient. All patients received gonadal hormones in addition.

The authors evaluated the results mainly on clinical ground, i.e., reappearance of menstrual periods and improvement of general condition. Preoperative and posttreatment laboratory investigation consisted in determination of ovarian and adrenal metabolites and basal metabolic rate. A strict correlation was found to exist between clinical improvement and normalization of the excretion pattern of ovarian metabolites. No changes were noted in the excretion of adrenal metabolites and basal metabolic rate. In 16 of 66 patients favorable results are still present 1 year after the last implantation. In 39 patients the treatment resulted in a complete failure. Partially positive results were noted in the remaining 11 cases. The best results were obtained in the group with simple hypophysial hypogonadism.

—*Maria Serratto, M.D.*

Further Studies on the Effect of Ribonucleic Acid on Homotransplantation Tolerance. FRANKLIN L. ASHLEY, EARL G. MCNALL, ROBERT F. SLOAN, N. R. DUTT, and EUGENE N. GARCIA. *Plast. & Reconstr. Surg.*, 1960, 26: 530.

HOMOGRAFT TOLERANCE may be induced by the injection of the recipient animal with viable cells derived from the blood, the spleen, and the thymus before grafting. Billingham and his associates showed that fractions containing polysaccharides or desoxyribose nucleic acid or polysaccharide complexes were responsible for the homograft immunity induced by nuclear preparations. Recently, the authors have reported that ribonucleic acid, RNA, derived from the visceral organs and from the skin of donor animals induced homograft tolerance. Oth and Castermans demonstrated that isolated nuclei lost homograft immunization activity if the RNA protein was extracted. In this article further information is presented concerning the role of RNA in homograft tolerance.

Randomly inbred colonies of Long Evans and Wistar rats were used as follows: the RNA was taken from two sources—the skin of neonatal LE rats and from the spleen, liver, and thymus of adult LE rats. The animals were switch-grafted by the Michel clip method at 22 days of age. The neonatal Wistar rats were injected intraperitoneally, whereas the LE rats remained uninjected. A control group of neonatal rats was also injected with saline and studied in similar fashion. Results showed that RNA isolated from both the skin and various visceral organs of Long Evans rats induced homograft tolerance when injected into recipient neonatal Wistar rats before the transplant of skin. The RNA derived from the thymus, spleen, and liver was quantitatively more effective than skin RNA in inducing to' rance.

An interesting finding was observed in that the donor Long Evans rats which were switch-grafted with skin from the RNA recipients, the Wistar rats, had an unexpected tolerance and longevity of the homograft, despite the fact that these rats had no neonatal preparation. The mechanism whereby this came to pass is not understood, although several theories are suggested by the authors.

—*Carl Schiller, M.D.*

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